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New strategies and tools to fight antimicrobial resistance: A structural point of view

Antimicrobial resistance (AMR) is a serious public health crisis worldwide. The excess and improper use of antibiotics is increasing the number of reported resistant microbial strains, compromising the conventional clinical treatments. The World Health Organization (WHO) has declared AMR a health emergency and has announced that the deaths attributable to AMR every year will be of 10 million in 2050, exceeding all the other major causes of death. To respond to AMR threat, an immediate action is required. Structural insights of key molecular players of AMR are fundamental for a deeper understanding of antimicrobial resistance and for the exploration of alternative therapeutic strategies. A group of six scary nosocomial pathogens is named with the acronym 'ESKAPE' because capable of 'escaping' the biocidal action of antibiotics classified as highly important for human medicine. ESKAPE increase frequency of treatment failures and severity of human infections by adapting to altered environmental conditions and by acquiring resistance determinants [1,2]. Among ESKAPE bacteria, three are most problematic, the highly resistant Gram-negative (Gram -) *K. pneumoniae, P. aeruginosa* and *A. baumannii*, typically associated with infections in severely ill hospitalized patients [3]. As in other bacteria, their cell envelope shield is the first line of defence against stress conditions and is crucial to resistance to antibiotics. This complex structure exposes two important barriers: capsule polysaccharides (CPS) and lipopolysaccharides (LPS). We have identified several CPS depolymerases synthesized by *K. pneumoniae* bacteriophages [4,5,6] and we have shown that they are effective against native capsule of specific clinical *K. pneumoniae* strains and significantly inhibit Klebsiella-induced mortality in a time-dependent manner. We also proposed the first structural characterization of a CPS depolymerase, named KP32gp38, encoded by a bacteriophage against *K. pneumoniae* (K-type 21 CPS) [7]. Recently, other phage depolymerases directed against hypervirulent strains (K-type 1 and K-type 2 CPS) of *K. pneumoniae* have been structurally characterized [8,9]. Structural and functional data on these cell envelope depolymerases will be presented as a tool for novel therapeutic development against AMR.

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