MS03-2-5 Structural and molecular characterization of the aminoglycoside phosphotransferase APH(3')-IIb from Pseudomonas aeruginosa
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Abstract
The World Health Organization (WHO) has warned on the importance to find new strategies to encounter the major health problem that is the antimicrobial resistance [1]. Bacterial pathogens have been classify in different groups function of there threat, Priority-1 group includes gram negative bacterial pathogens such as *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Acinetobacter baumannii* and *Enterobacteriaceae*. Aminoglycosides are broad spectrum antibiotics reserved for severe infections, most of the time associated with Priority-1 bacteria. They are characterize as bactericidal, concentration-dependent, and show a marked post-antibiotic effect [2].
However, bacteria have developed different mechanisms of resistance to these antibiotics. One of the most important mechanism is the expression of Aminoglycosides Modifying Enzymes (AME). These enzymes are able to inactivate aminoglycosides leading to a decreased affinity for their ribosomal target [3]. This modification is the major source of resistance against this class of antibiotics [4]. Among this class of enzymes we can notice the Aminoglycosides Phosphotransferases (APH). They catalyze the transfer of the γ-phosphate of a nucleotide (ATP or GTP) on a free hydroxyl group of an aminoglycoside. Structural and biochemical characterization are crucial to better understand this class of enzyme and develop effective inhibitors to circumvent their activity and to thus rejuvenate the antibacterial action of the aminoglycosides [5]. There have been significant advances providing structural, mechanistic, and inhibitory insights into many members of the aminoglycoside phosphotransferases (APHs) family [for example, 6;7].
In the present work and for the first time, we have solved the structure of the APH(3')-IIb of *P. aeruginosa* alone and in presence of MgATP and Kanamycin, two of its natural ligands. We have characterized its catalytic specificities and affinity for aminoglycosides and for phosphate donors. Preliminary results, obtained on the inhibition of this enzyme in order to resensitize bacteria to these antibiotics, would also be presented. Our results will be discussed from the of the drug resistances observed in clinical therapy, as well as the potential ways for reversing them. This work was supported by an ANR contract (SIAM project, ANR-19-AMRB-0001-01).

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