INVITED LECTURE

Studies on the Molecular Recognition of aminoglycoside antibiotics by RNA and Resistance Enzymes

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Aminoglycosides are highly potent, broad-spectrum antibiotics widely used in clinics. These drugs bind specifically to the bacterial decoding site, in the 16S ribosomal RNA (A-site), and thereby interfere with the accuracy of protein synthesis, leading to bacterial cell death. Additional targets such as the DIS kissing-loop complex, the Tat-responsive element and the Rev-responsive element, have been identified within the HIV genomic RNA and are also located in different functionally relevant RNA fragments, including self-splicing ribozymes and tRNAs. In addition, to specifically interact with RNA receptors, aminoglycosides are also recognized by the enzymes involved in antibiotic inactivation that play a central role in bacterial resistance processes. These proteins represent primary pharmacological targets. The emergence of high-resolution structural data for aminoglycoside/protein and /RNA complexes, during last decade, has greatly stimulated the structural based design of new bioactive derivatives with improved properties. More specifically, research has been focused on the preparation of tighter and more specific RNA binders, enzymatic inhibitors and new drugs non susceptible to enzymatic inactivation. Unfortunately, design efforts have frequently met a limited success, which, in our opinion, partially reflects our incomplete understanding of the molecular forces that stabilize the aminoglycoside complexes at a fundamental level.

Herein, we analyze several key aspects of the aminoglycoside recognition by RNA and proteins employing a pluridisciplinar approach that includes molecular modeling, organic synthesis, combinatorial chemistry and different biophysical techniques. The implications of our results for the design of improved amionglycoside-based ligands will be discussed.

References

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