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Editorial

Why Some Functional RNAs Such as Bacterial Riboswitches are Versatile Targets for Antibacterial Drug Discovery?

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In the last decade, multidrug and particularly the extended drug resistances have become a serious threat to public health worldwide [1]. The constantly rising number of reports on multidrug and extended resistances in a wide variety of human pathogenic bacterial strains reinforces the urgent need for the rapid development of new antibacterial drugs [2]. Therefore, we need to invent novel strategies for antibacterial drug development that are faster and more productive than the existing ones based on small molecules. To achieve this, we may need to employ new molecular targets and novel mechanisms of drug action. Promising new antibacterial drug targets are various functional RNAs such as ribozymes and riboswitches, which are essential parts of the DNA-RNA-protein machinery [3]. In contrast to proteins that are usually targeted by small molecules using their 3D-structures only, the functional RNAs such as riboswitches can be targeted not only by small molecules based on their 3D-structures but also with antisense oligonucleotides (ASOs) using their primary sequences. This provides a variety of methods and approaches in the search for novel therapeutics when targeting bacterial riboswitches [4,5]. They are usually found in the 5'- untranslated region (UTR) of the bacterial mRNA where they sense the presence of specific metabolites or ions. Currently, there are nearly 40 different classes of riboswitches that are classified based on the structure and specificity of their aptamer domains, which bind to a specific metabolite. Because of the specific binding, the riboswitches usually go under conformational changes and regulate the gene expression via two main mechanisms, namely, transcriptional termination and prevention of translation. Some of the riboswitch classes are widely distributed throughout the organisms such as TPP, AdoCbl, SAM-I/SAM-IV, C-di-GMP-I, and Glycine, while others are more narrowly distributed - Moco, SAH, Mg^{2+}, guanidine-II and NiCo. Depending on the pathogenic resistant bacteria of interest, researchers can choose among various riboswitch classes and target a conservative sequence (motif) that is found either in many or only in one bacterium. Bioinformatics analyses can easily predict the secondary structure of the mRNA, which will be further helpful for the design of the novel antibacterial drug candidates based on various types of ASOs by choosing an unpaired target sequence that is not present in the human genome. To facilitate the bacterium penetration ASOs are usually attached to cell-penetrating oligopeptides. There are three different generations of ASOs, each of which has different types of chemical modifications and therefore, different biochemical and pharmacokinetic properties. Thus, functional RNAs are versatile drug targets that can be inhibited not only by small molecules but also by ASOs, which can significantly speed up the process of antibacterial drug discovery.

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