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RNA as A Potent Target for Antibacterial Drug Discovery

Katya B Popova, Lozena A Otcheva, Martina Traykovska and Robert Penchovsky*

Department of Genetics, Sofia University "Saint Kliment Ohridski", Bulgaria

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***Corresponding author:** Robert Penchovsky, Department of Genetics, Faculty of Biology, Sofia University "Saint Kliment Ohridski", Bulgaria

Abstract

The development of novel antibiotics is becoming a real emergency due to the growing number of multidrug-resistant pathogenic bacteria. This is also a global problem due to mass production and application of various antibiotics both in human and veterinary medicine. Therefore, we need not only to create novel antibiotics but also to speed up the development pipeline. This may be achieved by using novel targets for antibacterial drug discovery. In this review, we focus our attention on several different types of RNA molecules that have been used as antibacterial drug targets. The RNA is the most ambiguous biopolymer in the cell, which carries many different functions. For instance, tRNAs, rRNAs, and mRNAs are essential for gene expression both in the pro-and eukaryotes. However, all these types of RNAs have sequences and something 3D structures that are specific for bacteria only and can be used to shut down essential biochemical processes in bacteria only. All these features make RNA very potent target for antibacterial drug development.

Keywords: rRNA; tRNAs; mRNA; Riboswitches; Drug Targets; Antibiotics; Antibacterial Drug Discovery

Abbreviations: FMN: Flavin Mononucleotide; TPP: Thiamine Pyrophosphate; SAM: S-Adenosylmethionine; tRNA: Transfer RNA; mRNA: Messenger RNA; rRNA: ribosomal RNA; BNSF: Bulgarian National Science Fund

Introduction

RNA is a unique and essential ingredient of life because it can execute very diverse and important functions, unlike any other biopolymer and can be used as a molecular target for the development of many different drugs [1]. RNA can carry and transfer a genetic information from DNA to proteins by messenger RNA (mRNA) and transfer RNA (tRNA). It also can regulate gene expression by riboswitches as a part of some mRNAs by directly binding specific cellular metabolites by work as a biosensor. RNA can also execute a catalytic function by ribozymes and ribosomal RNA (rRNA). Various types of RNAs, including rRNA, tRNA, ribozymes, and riboswitches carry sequences that are specific for bacteria and are not present in humans. In fact, many of those RNAs are essential for the bacterial cell and are found in many human pathogenic bacteria. Therefore, they can have applied them as molecular targets for antibacterial drug discovery [2]. In this mini-review, we focus attention on the most important features of rRNAs, tRNAs, a ribozyme such as RNase P, and riboswitches as potent antibacterial drug targets.

Major Types of RNA Targets for Antibacterial Drug Targets

Ribosomal RNAs

The ribosome is the most complex organelle in any living cell. It is responsible for peptide synthesis, which is essential for any bacteria [3]. Although the ribosome is a universal organelle and has a common general architecture, it is the most used antibacterial drug target because there are certain differences between prokaryotic and eukaryotic ribosomes. Exploiting those differences we can inhibit only the prokaryotic ribosome and keep the function of eukaryotic ribosome intact. The majority of known antibiotics exert their effects through interactions with the bacterial rRNAs, which are distinct from their eukaryotic counterparts. As a part of the ribosome, the bacterial rRNAs provide the frame onto which the ribosomal proteins are assembled, and generally direct ribosome function. In fact, the ribosome has been proven to be a ribozyme-based on a 3D structural analysis. This means that only rRNAs

are involved in the formation of the peptide bond during protein synthesis. The bacterial ribosome is built of two different subunits names 30S and 50S. When they come together a functional 70S ribosome is assembled.

The two mostly targeted rRNAs are 16S and 23S. The two main classes of antibiotics associating with the 16S rRNA are the aminoglycosides and the tetracyclines. Usually, antibiotics that target the 16S rRNA inhibit translation initiation or impair translation elongation either by blocking tRNA binding to the ribosome or preventing ribosome translocation along the mRNA. In addition, such antibiotics can affect translational proofreading. These effects are due to the fact that 16S rRNA takes part in the formation of three important sites of the ribosome. These sites are the A-site for binding of aminoacyl-tRNAs, the P- site for binding f-Met-tRNA for initiation of translation and the E-sites for a tRNA ejection. In contrast, 23S rRNA is responsible for the formation of the catalytic core of the ribosome. It makes a peptidyl transferase center (PTC) that directs peptide bond formation. Most antibiotics associating with the 23S rRNA bind to the PTC, which encompasses part of the A- and P-sites and inhibit the peptide bond formation. Such antibiotics include linezolid, erythromycin, chloramphenicol, and clindamycin. Unfortunately, there are resistant strains of pathogenic bacteria against all antibiotics that target bacterial rRNAs. Since the 3D structure of the bacterial ribosome is known, it is possible to pursue rational drug design based on various in silico modelling techniques.

Targeting Bacterial Trnas Synthesis

Transfer RNAs are essential elements of the protein translation process because they are required for decoding the information of mRNA by providing specific amino acids during the peptide synthesis in the ribosomes [4]. If we are able to inhibit the synthesis of tRNAs that are responsible for decoding one or more amino acids we will be able to shut down the whole peptide synthesis, which is going to be lethal for any living cell. A major issue with tRNA inhibition is due to the fact that the tRNAs are essential in both eukaryotic and prokaryotic organisms. Thus, tRNA -based antibiotics have to target aspects of tRNA synthesis/function that are unique to bacteria only. For the time being, there are molecules identified that inhibit different steps in bacterial rRNA production and function, including tRNA maturation, tRNA charging, and also tRNA-mediated decoding. Although few of these molecules have found clinical application as antibiotics. Such antibiotics are neomycin B that blocks the pre-tRNA processing and mupirocin that inhibit tRNA aminoacylation. Bacterial RNase P is also used as a target to block pre-tRNA processing since its function is necessary for the maturation of certain tRNAs.

Riboswitches as Antibacterial Drug Targets

Riboswitches are cis-acting gene-control elements that typically reside in the 5'-untranslated region (5'-UTR) of bacterial mRNAs [5]. They consist of two functional components, which are a metabolite-binding domain usually called aptamer and an expression platform. The aptamer forms a precise three-dimensional structure with a binding pocket, which senses the concentration of a specific metabolite and selectively binds to it. The riboswitches are classified based on their aptamer domain. They control gene expression by the termination of translation, prevention of translation, or, in the case of glmS riboswitch/ribozyme, via mRNA destabilization. There are 17 different classes of riboswitches that are found in over 40 different human pathogenic bacteria. Many riboswitches control biosynthetic pathways of essential cellular metabolites such as flavin mononucleotide (FMN), lysine, thiamine pyrophosphate (TPP), purines (adenine and guanine), S-adenosylmethionine (SAM) and many others. Not all riboswitches are suitable drug targets due to existing alternative biosynthetic pathways that are not under riboswitch control and/or alternative metabolite importing proteins. Some of the riboswitches such as FMN are proven antibacterial drug targets. However, there are still missing marketed antibiotics based on riboswitch-targeting molecules.

Discussion

Unlike proteins, which functions are executed by their 3D structures only, RNA can work in the cell not only through its 3D structures but also through its primary sequence. Because that, we can apply much more different mechanisms (methods) to inhibit specifically certain RNAs than that for protein inhibition. For instance, we can use small molecules that specifically bind to 3D RNA structures such as riboswitches, rRNAs, tRNAs, ribozymes like RNase P, and others. In addition, we have applied RNA inhibition methods that target specific primary sequences. Such methods include applications of various types of antisense oligonucleotides and RNase P-mediated RNA decay. These primary sequences targeting RNA-inhibition methods are based on well-understood rational rules and, therefore, they can be easily applied. Some RNAs have sequences that are found in many pathogenic bacteria while other RNAs carry unique sequences that are present only in a specific sort of human pathogenic bacteria. Therefore, certain types of RNA molecules can be used as targets for the development of broad-spectrum antibiotics while other types of RNAs can be targeted to develop narrow-spectrum antibiotics.

Conclusion

RNAs are diverse biopolymers that have many different essential functions in the bacterial cell. Such RNAs include rRNAs, mRNAs with riboswitches, and tRNAs. Many of these RNAs possess sequences and/or build structures that are specific bacteria and therefore can be employed as molecular targets, for antibacterial drug discovery and development. For the time being, rRNAs are mostly used as an RNA target for various types of marketed antibiotics. Transfer RNAs are targeted by several approved antibiotics while the riboswitches are not sill applied as a target by any marketed drug. Beyond any doubt in many instances, RNA is a very suitable antibacterial drug target. We expect that new classes of antibiotics can be developed based on specific RNA targeting by small molecules or by antisense-based approaches. This can address the growing problem with the multidrug-resistant strains of human pathogenic bacteria [6].

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