



Review

Non-coding RNAs as antibiotic targets



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ABSTRACT

Antibiotics inhibit a wide range of essential processes in the bacterial cell, including replication, transcription, translation and cell wall synthesis. In many instances, these antibiotics exert their effects through association with non-coding RNAs. This review highlights many classical antibiotic targets (e.g. rRNAs and the ribosome), explores a number of emerging targets (e.g. tRNAs, RNase P, riboswitches and small RNAs), and discusses the future directions and challenges associated with non-coding RNAs as antibiotic targets.

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1. Introduction

Historically, infectious disease has been a major cause of human morbidity and mortality. Antibiotics were first discovered in the early 1900's [1], and their subsequent wide-spread application has revolutionized health-care, and with it, improved our quality

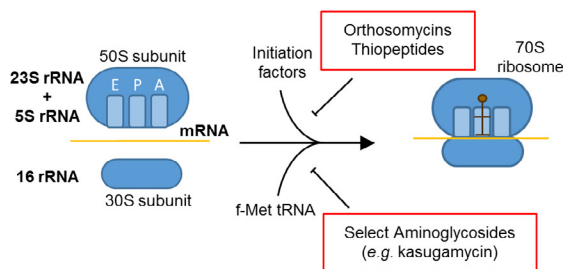
of life. Our ability to readily treat infections is, however, being steadily eroded with the rise in antibiotic resistance [2]. Consequently it is critical that we continue to search for new antibiotics, and devise innovative strategies to combat infectious disease.

Antibiotics – or more specifically for the purposes of this review, antibacterials – target a range of essential cellular processes, including DNA replication, transcription, translation and cell wall synthesis, among many others [3]. Despite a tendency to take a protein-centric view of the cell, non-coding RNAs are central to many of the processes currently targeted by antibiotics. As we

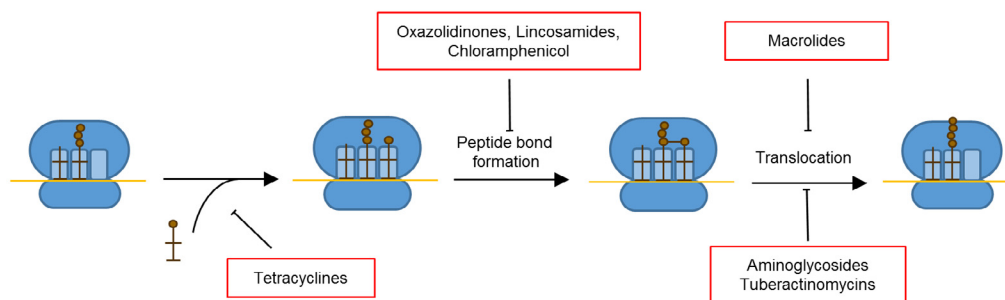
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A. Antibiotics targeting translation initiation



B. Antibiotics targeting translation elongation



C. Antibiotics affecting translation fidelity

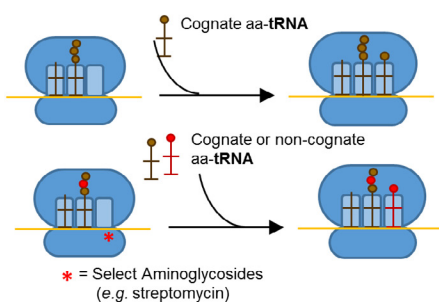


Fig. 1. Ribosome-targeting antibiotics. Schematic of ribosome activity, highlighting the points at which different antibiotics act. Throughout, antibiotics interacting with the 23S rRNA are shown above the ribosome, while those binding the 16S are indicated below the ribosome. (A) Antibiotics targeting translation initiation. During translation initiation, the 50S (containing the 23S rRNA) and 30S (containing the 16S rRNA) ribosomal subunits come together on the mRNA template, forming a 70S ribosome. This process requires the binding of initiation factors, and the binding of the f-Met-tRNA to the P site of the ribosome. The orthosomycins and thiopeptides (binding to the 23S rRNA) prevent binding of initiation factors to the ribosome, while kasugamycin and edeine (binding to the 16S rRNA) prevent the binding of the f-Met-tRNA. (B) Antibiotics targeting translation elongation. There are multiple stages of translation elongation that are targeted by antibiotics. The tetracyclines bind the 16S rRNA and block the addition of new aminoacyl-tRNAs into the A-site. Linezolid, clindamycin, and chloramphenicol (binding to the 23S rRNA) block peptide bond formation. Finally, the aminoglycosides and tuberactinomycins (binding to the 16S) and erythromycin (binding to the exit channel) block translocation. (C) Antibiotics that affect translation fidelity. The decoding centre of the 16S rRNA allows only cognate tRNAs to enter the A site, ensuring accurate translation. Paromomycin and streptomycin bind to the decoding centre such that either cognate or non-cognate tRNAs are accepted into the A site, resulting in mistranslation (illustrated by the incorporation of red amino acids).

continue to learn more about the function of non-coding RNAs in the bacterial cell, we are presented with opportunities to exploit this understanding, and develop new and/or improved ways of controlling bacterial growth and pathogenesis.

Here we explore the mechanisms by which antibiotics target non-coding RNAs in bacteria, from the classical rRNAs and tRNAs, through to the more recently discovered regulatory RNAs. For each RNA class, we highlight past and present drug discovery and development efforts, and discuss future perspectives and challenges associated with non-coding RNA activity modulation.

2. rRNA – the most-targeted system in a bacterial cell?

Protein translation is an RNA-driven process involving three major RNA classes: messenger RNAs (mRNAs), transfer RNAs

(tRNAs) and ribosomal RNAs (rRNAs) (Fig. 1). Translation takes place within the ribosome, which is a massive ribonucleoprotein complex comprising three rRNAs and over 50 proteins [4,5]. These components are divided between two subunits: the 50S subunit containing the 23S and 5S rRNAs, and the smaller 30S subunit containing the 16S rRNA. These two subunits come together when translation initiates, forming the mature 70S ribosome.

Translation encompasses three stages: initiation, elongation, and termination [6,7]. The first stage involves assembling the 70S ribosome on the mRNA transcript, and positioning it in frame so translation can initiate (Fig. 1A). Elongation next requires the amino acid-bearing tRNAs to cycle through three positions within the ribosome: the A-, P-, and E-sites (Fig. 1A,B). Incoming aminoacyl-tRNAs (aa-tRNAs) first localize to the A-site, or aminoacyl site, where they pair with their cognate codon on the mRNA

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