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Thiopeptide Antibiotics Act on Both Host and Microbe to Deliver Double Punch on Mycobacterial Infection

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Abstract

Mycobacterial infection has long been one of the most serious infectious diseases throughout the world. Since the abuse of antibiotics, and for other reasons, the emergence of bacterial drug-resistance is now one of the most urgent clinical problems. Nowadays, the speed of antibiotic development is actually far more slowly than that of the bacterial drug-resistance generation. Thereby, searching for new efficient antibiotics is a top priority in pharmaceutical studies. In this commentary, we summarized the recent advances regarding the development of new thiopeptide antibiotics via biosynthetic strategy and the discovery of a novel dual mechanism of action against *Mycobacterium marinum*-represented intracellular pathogens.

Keywords: Mycobacterial infection; Thiopeptide antibiotics; Thiostrepton derivatives; Autophagy; Dual mode of action

Introduction

Infectious diseases, the second leading cause of death worldwide, exert a grave threat to the public health. This situation is aggravating due to the progressively emerging microbial resistance and the lack of new drugs into the clinic [1,2]. Mycobacterial infection has had its notorious name engraved on the Georgia Guidestones. For instance, human tuberculosis, which is mainly caused by *Mycobacterium tuberculosis*, causes approximately more than 1.5 million deaths each year [3]. The stinky devil shows no regret in escalating its influence and evolves multidrug-resistant tuberculosis levering up the costs of corresponding treatment [4,5]. It brooks no delay to search for effective drugs against [6].

Natural products remain a major source for antibiotic discovery and drug development [7-9]; however, the accessibility and efficiency for chemical synthesis of these compounds, as well as the associated investigation into their mechanisms of action, often get choked by challenges arising from the structural complexity. Synthetic chemists and pharmaceutical chemists have their own opinions to develop anti-infective agents, while extracting untapped functions from existing drugs is outcropping as an accepted and efficient way. During the *in vitro* screen of new anti-tuberculosis agents amongst known drugs, an archetypal thiopeptide antibiotic, thiostrepton, showed to behave a remarkable bioactivity against either wild type or multidrug-resistant *M. tuberculosis* with a very low minimum inhibitory concentration [10]. Thiostrepton has long been wildly used as an animal feed additive, and no obvious side effects caused by thiostrepton have been reported. Unfortunately, the drawbacks of thiopeptides (e.g., poor aqueous solubility and pharmacokinetics) limited their potential clinical applications [11]. As synthetic biologists, we sought to make a stunning turnaround via a biosynthetic strategy to obtain more potent thiopeptide antibiotics with improved pharmaceutical properties [12,13].

In the previous work, we developed a robust and efficient chemo-enzymatic protocol to synthesize quinaldic acid and its analogs, which serve as key building blocks in the biosynthetic pathway of Thiostrepton [14]. As a "chemical module" in synthetic biology, the produced quinaldic acid analogs could be incorporated into Thiostrepton skeleton via. a mutational biosynthesis strategy and used for replacing multiple gene functions [15]. The obtained thiosrtepton derivatives that varied with respect to the quinaldic acid moiety of the side ring (Figure 1) possessed improved antibacterial activity and water-solubility [16].

Meanwhile, utilizing these obtained thiopeptide molecules as chemical probes and drug leads to treat the zebra fish infected by intracellular pathogen *M. marinum* (an important model strain of *M. tuberculosis* used in lab), we uncovered a unique mode of action of TSR-type antibiotics against parasitic mycobacteria [17]. In addition to directly targeting the ribosome of bacterial parasites, TSRs can induce autophagy to enhance host cell defense by activating Endoplasmic Reticulum (ER) stress and Unfolded Protein Response (UPR) pathways in eukaryotes (Figure 2). This unusual property of TSR is most likely attributed to its role as a dual functional inhibitor for both prokaryotic ribosomes and eukaryotic proteasomes.

Although a number of endoplasmic reticulum stress inducers and ribosome inhibitors are reported and some of them have been developed into clinically utilized first-line drugs [18,19], to our best knowledge, thiostreptonss are the only type of antibiotics that intuitively act on both the bacterial pathogens and infected cells. Distinct from the current antibacterials used in clinic that only affect bacterial cells, thiostreptons activate autophagy that plays a key role in host antimicrobial immunity [20,21], to eliminate intracellular pathogens parasitizing host macrophages. Several molecular mechanisms have been gained by *M. tuberculosis* or other intracellular

pathogens to prevent the host cell from activating autophagy during the process of evolution [22,23].

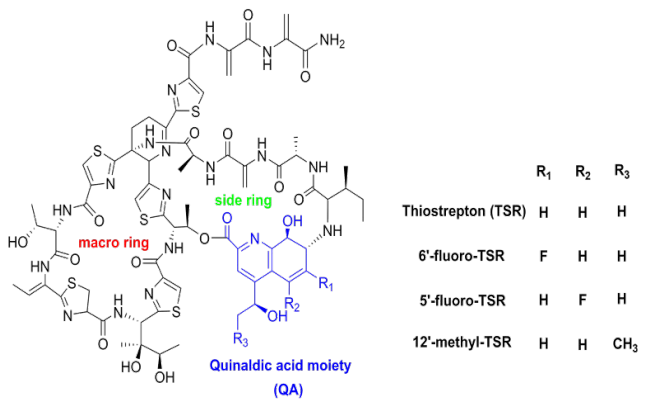

Figure 1: Chemical structures of thiostrepton (TSR) and its side ring-modified derivatives (6'-fluoro-TSR, 5'-fluoro-TSR, and 12'-methyl-TSR) that vary in quinaldic acid (QA) substitution; the QA moiety in the structure is indicated in blue.

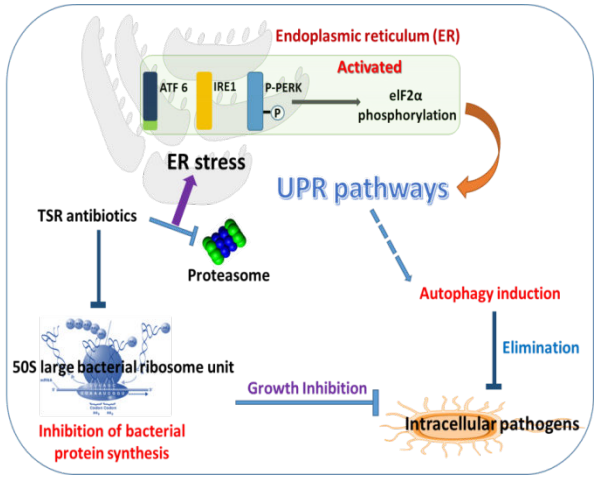

Figure 2: TSR antibiotics exhibite a dual mode of action against intracellular pathogens that involves effects on both the host and the microbe.

However, it will be hard for bacteria to generate resistance against Thiostrepton-type antibiotics that can deliver a double punch by acting on two totally different targets. This newly elucidated dual mode of action may inspire the future changes in the treatment of intracellular pathogens by taking host response into account, and facilitate developing new drugs for clinical applications in dealing with mycobacterial diseases. Meanwhile, recent developments in drug delivery systems will also accelerate the upcoming clinical use of thiopeptide antibiotics with large molecular weights and poor water solubilities [24,25].

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