Mycobacterial Diseases

Zheng and Liu, Mycobact Dis 2016, 6:1
http://dx.doi.org/10.4172/2161-1068.1000203

Commentary open access journal

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

Qingfei Zheng[1*] **and Wen Liu**[1,2*]

[1]*State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai, China*

[2]*Huzhou Center of Bio-Synthetic Innovation, Huzhou, China*

[*]**Corresponding author:** Zheng Q, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China, Tel: +86-21-54925539; E-mail: zhengqf@sioc.ac.cn

Liu W, Huzhou Center of Bio-Synthetic Innovation, Huzhou, China, Tel: +86-21-54925111; E-mail: wliu@mail.sioc.ac.cn

Received date: February 26, 2016; **Accepted date:** March 14, 2016; **Published date:** March 25, 2016

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].

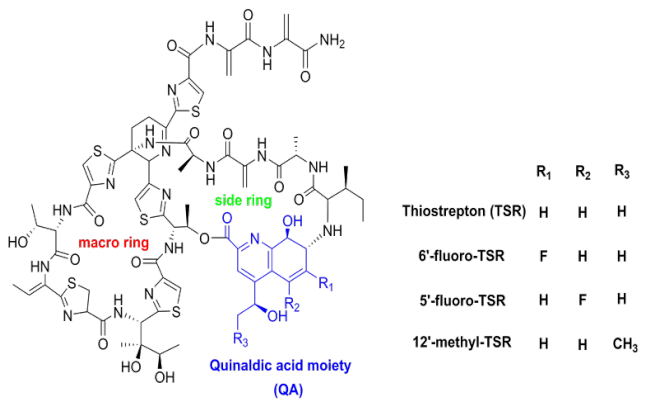

Figure 1: Chemical structures of thiostrepton (TSR) and its side ring-modified derivatives (6'-fluoro-TSR, 5'-fluoro-TSR, and 12'-methyl-TSR) that vary in quinaldic acid (QA) substitution; the QA moiety in the structure is indicated in blue.

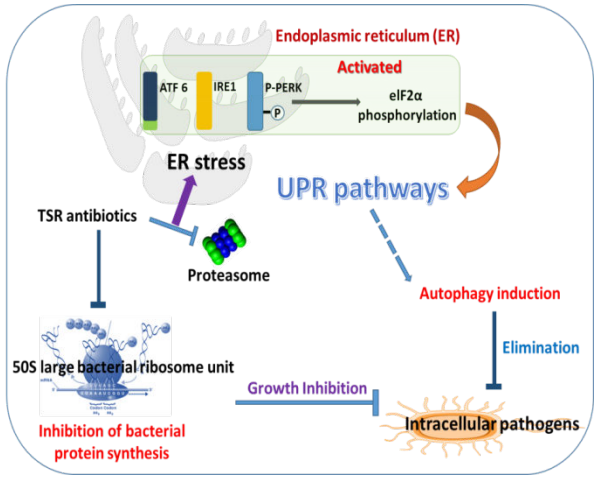

Figure 2: TSR antibiotics exhibite a dual mode of action against intracellular pathogens that involves effects on both the host and the microbe.

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].

References

1. Tompkins DM, Carver S, Jones ME, Krkosek M, Skerratt LF (2015) Emerging infectious diseases of wildlife: a critical perspective. Trends Parasitol 31: 149-159.
2. Laxminarayan R, Duse A, Wattal C, Zaidi AK, Wertheim HF, et al. (2013) Antibiotic resistance-the need for global solutions. Lancet Infect Dis 13: 1057-1098.
3. Anon (2011) Global tuberculosis control: WHO report 2011. World Health Organization.
4. Gumbo T (2013) Biological variability and the emergence of multidrug-resistant tuberculosis. Nat Genet 45: 720-721.
5. Yates TA, Khan PY, Knight GM, Taylor JG, McHugh TD, et al. (2016) The transmission of Mycobacterium tuberculosis in high burden settings. Lancet Infect Dis 16: 227-238.
6. Zumla A, Nahid P, Cole ST (2013) Advances in the development of new tuberculosis drugs and treatment regimens. Nat Rev Drug Discov 12: 388-404.
7. Paterson I, Anderson EA (2005) Chemistry. The renaissance of natural products as drug candidates. Science 310: 451-453.
8. Newman DJ, Cragg GM (2012) Natural products as sources of new drugs over the 30 years from 1981 to 2010. J Nat Prod 75: 311-335.
9. Barry CE (2014) Tuberculosis: Drug discovery goes au naturel. Nature 506: 436-437.
10. Lougheed KE, Taylor DL, Osborne SA, Bryans JS, Buxton RS (2009) New anti-tuberculosis agents amongst known drugs. Tuberculosis (Edinb) 89: 364-370.
11. Bagley MC, Dale JW, Merritt EA, Xiong X (2005) Thiopeptide antibiotics. Chem Rev 105: 685-714.
12. Zhang Q, Liu W (2013) Biosynthesis of thiopeptide antibiotics and their pathway engineering. Nat Prod Rep 30: 218-226.
13. Wang S, Zhou S, Liu W (2013) Opportunities and challenges from current investigations into the biosynthetic logic of nosiheptide-represented thiopeptide antibiotics. Curr Opin Chem Biol 17: 626-634.
14. Zheng Q, Wang S, Liu W (2014) Discovery and efficient synthesis of a biologically active alkaloid inspired by thiostrepton biosynthesis. Tetrahedron 70: 7686-7690.
15. Wang S, Zheng Q, Wang J, Chen D, Yu Y, et al. (2016) Concurrent modifications of the C-terminus and side ring of thiostrepton and their synergistic effects with respect to improving antibacterial activities. Org Chem Front 3: 496-500.
16. Wang S, Zheng Q, Wang J, Zhao Z, Li Q, et al. (2015) Target-oriented design and biosynthesis of thiostrepton-derived thiopeptide antibiotics with improved pharmaceutical properties. Org Chem Front 2: 106-109.
17. Zheng Q, Wang Q, Wang S, Wu J, Gao Q, et al. (2015) Thiopeptide Antibiotics Exhibit a Dual Mode of Action against Intracellular Pathogens by Affecting Both Host and Microbe. Chem Biol 22: 1002-1007.
18. Pereira DM, Valentão P, Correia-da-Silva G, Teixeira N, Andrade PB (2015) Translating endoplasmic reticulum biology into the clinic: a role for ER-targeted natural products? Nat Prod Rep 32: 705-722.
19. Wilson DN (2014) Ribosome-targeting antibiotics and mechanisms of bacterial resistance. Nat Rev Microbiol 12: 35-48.
20. Deretic V, Levine B (2009) Autophagy, immunity, and microbial adaptations. Cell Host Microbe 5: 527-549.
21. Gomes LC, Dikic I (2014) Autophagy in antimicrobial immunity. Mol Cell 54: 224-233.
22. Baxt LA, Garza-Mayers AC, Goldberg MB (2013) Bacterial subversion of host innate immune pathways. Science 340: 697-701.
23. Deretic V, Saitoh T, Akira S (2013) Autophagy in infection, inflammation and immunity. Nat Rev Immunol 13: 722-737.
24. Wang M, Gartel AL (2011) Micelle-encapsulated thiostrepton as an effective nanomedicine for inhibiting tumor growth and for suppressing FOXM1 in human xenografts. Mol Cancer Ther 10: 2287-2297.

25. Lehar SM, Pillow T, Xu M, Staben L, Kajihara KK, et al. (2015) Novel antibody-antibiotic conjugate eliminates intracellular S. aureus. Nature 527: 323-328.