Journal of Bacteriology and Virology 2017. Vol. 47, No. 2 p.102 – 104
http://dx.doi.org/10.4167/jbv.2017.47.2.102

Research Update (Minireview)

Texiobactin, a Potent Killer of Antibiotic Resistant Pathogens

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Antibiotic resistance is a major global concern that primarily affects public health. Texiobactin is a newly discovered antibiotic produces by soil microbes isolated from natural environment. Drug is active against Gram-positive bacteria as it inhibits biosynthesis of peptidoglycan. Infection of methicillin-resistant *Staphylococcus aureus* (MRSA) and *Streptococcus pneumoniae* in mice elicits a good response reduce bacterial load. Although extensive efforts have been made to discover new antibiotics but results are still not satisfactory to meet the demands of public health. Recently it has been shown that the discovery of texiobactin by iChip will be a great stone mile to discover more antibiotics.

Key Words: Texiobactin, Peptidoglycan, MRSA, iChip

INTRODUCTION

Antibiotics play a fundamental role for treatment of different health conditions. However the success of treatment is often hindered by antibiotic resistance. Drug discovery starts with penicillin discovery in 1940's (1). According to a survey of the Center for Disease Control and Prevention (CDC) reported that 2 million people are suffered with resistant bacteria every year (2). In this era of competitive clinical practice, where antibiotics are needed across the world, and sources of antibiotics are limited to discover a drug without resistance is a great approach (2). In soil there are many bacterial species; among that 99% cannot be cultured (2). Different methodologies like cultural, molecular and, 16S rRNA techniques have been used for microbial diversity (2). Soil dwelling bacteria *Actinomycetes*, spore forming genera have been staple source of antibiotic for a long period of time (3).

It has been reported a new antibiotic by the discovery of an uncultivable soil bacterium, known as texiobactin (1). This had been further explored and showed that texiobactin is produced by a new species of β-proteobacteria provisionally named *Eleftheria terrae*, a gram negative bacterium, that belongs to genus Aquabacteria (3). *Eleftheria terrae* and many other active bacteria that can also produce antibiotics refuse to grow in laboratory conditions, which are collectively known as microbial 'dark matter' (4). Recent advances in antibiotic discovery aids our understanding.

Use of iChip

Discovery of new antibiotics will be facilitated by iChip, as it only allows the antibiotics to be isolated from microorganisms in the natural environment which cannot grow

Received: June 12, 2017/ Revised: June 14, 2017/ Accepted: June 14, 2017
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**This research was supported by the 2017 scientific promotion program funded by Jeju National University.
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under laboratory conditions (1, 4). Here iChip is used to isolate antibiotic produced by the soil microorganisms (1). Membranes and plastic plates used in iChip, latter were having holes used to capture antimicrobial compounds (1, 3). One bacterial cell was allowed to each hole from soil sample dilution, and plates were covered with semi permeable membrane from both sides for proper diffusion and placed back in soil for one month (1, 3). After the production of colony, isolates that are not cultured otherwise can grow *in vitro* (1).

Texiobactin is effective against the pathogens without resistance. *E. tarrae* culture supernatant was partially purified and a compound known as texiobactin was obtained (1). By 16S rDNA genomic sequence it was confirmed that texiobactin is depsipeptide having methylphenylalanine, enduracididine and four D-amino acid that belongs to aquabacteria By the help of homology analysis gene cluster was recognized as it has two large non-ribosomal peptides known as *tox1* and *tox2* (1).

Antibacterial activity of texiobactin

From many years mehticillin resistant *Staphylococcus aureus* (MRSA) has been great threat for public due to antibiotic resistance and remains a major cause of mortality (5, 6). It is showed that texiobactin was effective against the representative strains of bacteria that cause wound and invasive infections e.g., *Staphylococcus aureus*, MRSA, *Streptococcus pneumoniae* and *Mycobacterium tuberculosis* (1). Interestingly, newly discovered drug showed very good activity against *Mycobacterium tuberculosis* as the composition of cell wall is different from gram positive bacteria (1). It composed of peptidoglycan and mycolic acid. Ethambutol is used to treat tuberculosis and inhibit synthesis of arbinoglactan while texiobactin has dual inhibitory effect on synthesis of peptidoglycan and as well as arbinoglactin (7). Texiobactin was effective in a single dose in mouse models for MRSA septicemia and pneumococcal pneumonia (3). Texiobactin is a better choice of drug as compared to vancomycin as it kills late exponential phase population of bacteria (1). Enterococci are commonly known as nonpathogenic commensal bacteria displaying low levels of virulence. However, their inherent characteristics allow the enterococci as an outstanding clinical problem (8). First of all, enterococci have the ability to resist different antimicrobial compounds. These nosocomial pathogens colonize in patients and cause vancomycin-resistant enterococci (VRE) infection (9). Enterococci also show survival for a longer period of time even in harsh conditions like heat and chlorine (9, 10). Vancomycin is active against enterococci while further investigations showed that texiobactin has bactericidal activity against enterococci (1, 11). Texiobactin was also highly effective against *Bacillus anthracis* and *Clostridium difficle* (1).

Mode of action

The mode of action of texiobactin differs from other antibiotics, as it inhibits peptidoglycan synthesis by binding to highly conserved lipid II and lipid III and penetrates into the cell. Lipid II is peptidoglycan precursor while lipid III is techoic acid precursor (1). In Gram-positive susceptible bacteria there is no texiobactin resistance (1). Peptidoglycan and lipids plays an important role in cell wall synthesis of bacteria. Bacteria is not resistant to texiobactin because antibiotics that hit lipid precursors are likely less resistant. Bacteria are more resistant to antibiotics that inhibit synthesis of protein because genes encoding target proteins can be mutated themselves. Further investigations showed that at four times of the minimal inhibitory concentration (MIC), no texiobactin resistant *S. aureus* or *M. tuberculosis* was found (1).

***In vivo* antibacterial activity of texiobactin**

Furthermore texiobactin was highly stable in presence of serum. Even single dose of texiobactin treatment cleared infection in mouse model.

Three mouse models of infection were shown to check potency of antibiotics (1). In septicemia protection model MRSA was used in mice for infection (1). To investigate the effect of compound in mice, colony forming units (CFU) were calculated. Likewise, study of texiobactin on thigh model of infection by *S. aureus*, exhibited good potency against infection. In disparity, lungs of mice showed reduc-

tion in CFU (1). These results suggest that texiobactin has good efficacy against *S. pneumoniae* (1).

Closing Remarks

A different strategy to culture uncultivable bacteria from their natural environment enables the development of new synthetic antibiotics, and also species specific antibiotics. Here we have summarized current discovery of texiobactin from uncultivable soil environment that has excellent bactericidal activity against gram positive bacteria and antibiotic resistant pathogenic bacteria. Further investigations shows that texiobactin inhibits synthesis of peptidoglycan by binding with lipid II and lipid III precursors of cell wall, target is not protein. Drug discovery from natural sources by iChip will be a great milestone in future to discover more antibiotics.

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