SHORT COMMUNICATION

Endolysin: A therapeutic alternative for antibiotic resistant pathogens causing urinary tract infections

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Urinary Tract Infections (UTIs) caused by pathogenic bacteria is the most frequent clinical condition affecting almost 150 million population each year worldwide, resulting in a huge economic losses due to clinical presentation. The UTIs treated with antibiotics show post treatment complications, which include repeated recurrence, pyelonephritis, renal damage, irreversible loss to kidney tissue during retrograde proliferation leading to severe risk of bacteremia with a major risk of antibiotic resistance due to recurring infections. Bacteriophage-encoded endolysin have been oftentimes recognized as a promising antibacterial agent to eradicate antibiotic-resistant bacteria due to their host specific nature and less chances of resistance development in bacterial pathogens. Endolysin kill bacterial pathogens by hydrolyzing peptidoglycan lyer in cell wall. Though large number of lytic enzymes has been reported against various MDR gram positive bacteria, very few reported against gram negative bacterial pathogens, due to their outer membrane, which acts as a barrier to cross by endolysin to hydrolyze peptidoglycan. Therefore, treatment of MDR gram negative pathogens through lytic enzymes is high challenging. However, engineering of endolysin by fusion of membrane rupturing protein can increase its access to the target site in cell wall. The fusion molecule will increase the host range and provide a path to treat common UTIs caused by gram negative and positive pathogens. This commentary is focusing on how, endolysin can be effectively modified to increase their efficiency against Multi drug resistant bacterial pathogens.

Key Words: *Urinary tract infections (UTIs); Endolysin; Multi drug resistance (MDR); Protein engineering*

DESCRIPTION

Urinary Tract Infections (UTIs) caused by common bacterial pathogens is the most frequent clinical condition affecting almost 150 million population each year worldwide [1], from a neonate to a geriatric individual [2]. UTIs resulted in 3.5 billion U.S $ per year economic losses due to clinical presentation of this disease.

Both gram negative and positive bacteria cause UTIs along with certain fungi [3]. Most common causative agent for UTIs is Uropthgenic Escherichia Coli (UPEC), while other pathogenic bacteria include Klebsiella pneumonia, Pseudomonas aeruginosa, Staphylococcus arophyicus and Staphylococcus aureus [4]. The improper and uncontrolled use of antibiotics has resulted in the development of antimicrobial resistance world-wide. Most of the patients with symptomatic UTIs opt for antibiotic treatment, which in the long run alter the normal microbial flora of reproductive tract and gastro intestinal tract hence leading to development of multidrug resistant pathogens. When the normal flora is disrupted by antibiotics, a gap in the niche is generated, which increase the risk of colonization of drug resistant uropathogenic bacteria causing a higher mortality rate [5].

Most importantly, MDR gram negative pathogens like clinical Klebsiella and Pseudomonas isolates has been nominated as major uropathogens in hospital acquired infections, which has raised therapeutic challenges [6, 7]. This increased incidence of drug resistant uropathogens is an emerging concern for medical fraternity due to limitation of treatment options, which are expensive and still does not avoid the risk of death due to systemic infection. In underdeveloped countries where health care system is not advanced and diagnosis is made without the availability of urine test culture or antimicrobial susceptibility, the emergence of MDR is spiking [8,9]. This continues emergence of MDR uropathogenic strains is mostly seen in the countries with low socioeconomic impact including poverty, ignorance, unhygienic practices and substandard drugs availability which worsen the situation in the health care management categorizing it a public health issue [10,11].

The increased microbial susceptibility of uropathogenens to antimicrobials is attributed to the fact that most of these gram negative pathogens falls under the classification of Extended Spectrum-Beta-Lactamases (ESBLs). These ESBLs presenting Gram Negative Bacteria (ESBLs-GNBs) are the primary culprits involved in UTIs leading to inflexibility of empirical treatment options which worsen the prognosis of condition. These ESBLs-GNBs purpose a significant challenge in the pragmatic antibiotic selection by physicians due to their resistance to wide range of antibiotics (aminoglycosides, cephalosporins and quinolones) [12,13]. The growing prevalence of these ESBLs gram negative uropathogens limit the treatment preferences and pose a unanimous public health implication [14]. The antibiotics are struggling to keep up the pace in this growing phase of pathogenic resistance and acquired mutations.

To provide an alternative therapeutic approach for UTIs, bacteriophage derived endolysins can be of high significance in terms of its efficacy and host specificity. The characteristic features of phage derived endolysin such as high binding specificity and a lower chance of developing resistance have provided promise for endolysins as potential antimicrobial agent [15]. To date, many phage endolysins have been successfully applied as antimicrobial agents to treat P. aeuroginosa, Enterococcus faecalis/faecium, Acinetobacter and E. coli. This kind of alternative may reduce the overuse of antibiotics in the future [16]. However, the major challenge in application of endolysin in the treatment of gram negative pathogens is the presence of outer membrane, which does not allow endolysin to reach cell wall, therefore, accessory proteins such holin are required to rupture the cell wall. Holin rupture the outer membrane to create pores, which allow endolysin to lyse peptidoglycan layer in cell wall [17].

In a recent study, Basit et al., expressed an engineered variant of endolysin from RL phage of Pseudomonas aeruginosa (MDR), by fusing holin at it N terminus. The engineered endolysin showed significant antibacterial activity against a wide range of clinically challenging MDR strains such as Pseudomonas aeruginosa, Klebsella pneumonia, E. coli and Methicillin Resistant Staphylococcus Aureus (MRSA), which are mainly involved

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involved in UTIs. The holin fused endolysin variant was more active than the simple endolysin, indicating that holin provide access to endolysin to hydrolyze bacterial cell wall [18]. Although many other membrane permeablizers have also been reported to increase lytic activity of endolysin against gram negative pathogens, however, their adverse effects on normal flora limit their in *vivo* clinical application. Therefore, fusion of holin with endolysin in different orientations will not only reduce the side effects on normal flora due its host specific nature, but also increase the bacterial killing efficiency. Various protein engineering methods such as directed evolution [19] or de novo protein design approach [20] can be employed to further enhance the bactericidal efficiency, thermal and pH stability of the holin fused endolysin, to assure their in *vivo* application in treatment of multi drug resistant UTIs.

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