Yanmin Hu et al., J Bacteriol Parasitol 2015, 6:4
http://dx.doi.org/10.4172/2155-9597.S1.010

OMICS International
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3rd International Congress on
Bacteriology and Infectious Diseases
August 04-06, 2015 Valencia, Spain

Antimicrobial peptide novicidin synergises with rifampicin, ceftriaxone and ceftazidime against antibiotic-resistant gram-negative *Enterobacteriaceae in vitro*

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Infections caused by gram-negative bacteria species such as those in the Enterobactericeae family are responsible for high rates of morbidity and mortality. The spread of antibiotic resistance amongst gram-negative pathogens is a serious clinical threat requiring urgent attention. Traditional novel drug development inevitably leads to emergence of new resistant bacterial strains, rendering the new drugs ineffective. Therefore reviving the therapeutic potentials of existing antibiotics represents an attractive novel strategy. Novicidin, a novel cationic antimicrobial peptide is effective against gram-negative bacteria. The actions of novicidin in combination with rifampicin, ceftriaxone and ceftazidime were investigated. We performed *in vitro* investigations to test against 94 antibiotic resistant clinical Gram-negative isolates and 7 strains containing New Delhi metallo-β-lactamase-1 (NDM-1). The effects of combining novicidin with rifampicin, ceftriaxone and ceftazidime were examined using the chequerboard method and time kill curves. A fluorescence assay was used to investigate the depolarisation of the bacterial cell membrane by novicidin. The post antibiotic effect was measured. The cytotoxicity and haemolysis of novicidin were examined using neutral red uptake in the L929 fibroblast cell line and lysis of human blood. Novicidin combined with rifampicin showed synergy with over 70% of the tested gram-negative clinical isolates (n=94) and NDM-1 strains (n=7) reducing the MIC significantly. The combination of novicidin with ceftriaxone and ceftazidime showed synergistic effects with more than 89.7% of ceftriaxone-resistant strains and 94.1% of ceftazidime-resistant strains. These synergistic combinations were also demonstrated using time kill studies with multiple strains. We also demonstrated that novicidin altered the cytoplasmic membrane potential by membrane depolarisation against both *Escherichia coli* and an isolate from the *Klebsiella-Enterobacter-Serratia* (KES) group. Furthermore, novicidin was shown to increase the post-antibiotic effect (PAE) when combined with rifampicin or ceftriaxone. Novicidin showed low haemolytic activity and conservation of cell viability in the cell culture post treatment. We demonstrated that novicidin strongly rejuvenates the therapeutic potencies of ceftriaxone or ceftazidime against ceftriaxone or ceftazidime resistant gram-negative bacteria *in vitro*. In addition, novicidin boosted the activity of rifampicin. This strategy can have major clinical implications in our fight against antibiotic resistance bacterial infections.

Biography

Yanmin Hu is a Senior Research Fellow at St George's, University of London. Her main research interests are in tuberculosis and antibiotic discovery. The scientific and intellectual imperatives for her research include new drugs and better drug regimen for tuberculosis and other important infectious diseases; improved chemotherapy to eradicate persistent bacteria; molecular approaches to understand the processes of infection and pathogenesis of *M. tuberculosis* and other pathogens.

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