Protein Cell 2010, 1(12): 1051–1052
DOI 10.1007/s13238-010-0134-7

Protein & Cell

NEWS AND VIEWS

Human in check: new threat from superbugs equipped with NDM-1

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Just one day after the official announcement for the end of H1N1 influenza by WHO, Kumarasamy et al. (2010) reported the emergence of a new global health problem, which was caused by Gram-negative *Enterobacteriaceae* with resistance to a broad range of beta-lactam antibiotics due to the presence of $bla_{\text{NDM-1}}$ that encodes NDM-1, which inactivates all β-lactam antibiotics. Now, the NDM-1 superbugs have been identified in multiple countries, including India, Pakistan, UK, USA, Japan, Brazil, Canada, Australia, France, Holland and China. A Belgian patient who was infected in Pakistan following a car accident became the first known fatality from NDM-1. NDM-1 belongs to metallo-β-lactamase (MBL), which is a characterized family of carbapenem antibiotics inactivating enzymes. However, the broad resistance to currently available antibiotics and the strong capability of contemporary horizontal gene transfer (HGT) bring the threat from NDM-1 bacteria into top news throughout the world. In the never-stopped game between human being and pathogens, we are in check again.

The first reported case was an India-originated Swedish patient who frequently traveled to India and acquired a urinary tract infection (Yong et al., 2009). Researchers isolated a carbapenem-resistant *Klebsiella pneumonia* 05-506. It possesses an MBL that hydrolyzes and inactivates carbapenem antibiotics, and has the broadest spectrum of antibacterial activity and are among the most important drugs to kill bacteria that are resistant to other antibiotics. However, the encoding gene was different from the known types of MBL genes, with only < 33% amino acid identity. The novel enzyme was named NDM-1 (New Delhi metallo-β-lactamase 1) because the patient was infected during clinical treatment at New Delhi, India. Genetic analysis revealed that the NDM-1 encoding gene, $bla_{\text{NDM-1}}$, located on a 180-kb plasmid, which also had two other antibiotic-resistance gene containing regions upstream of $bla_{\text{NDM-1}}$ fragment. The multi-drug resistant plasmid exhibited high horizontal gene transfer capability and could easily confer the antibiotic resistance to other strains; in addition, recombination could occur during transfer, which further promoted its spread to other bacterial hosts.

Antibiotic and antibiotic resistant genes are the two sides of same coin. Soon after the first use of antibiotics in medicine, resistant organisms were seen to arise during therapy. As is well-acknowledged, the discovery and application of penicillin is a significant milestone in medical history because it cured a variety of previously serious diseases, such as syphilis, rheumatic fever and cellulitis; especially during the World War II, the death caused by infectious diseases were markedly reduced by use of penicillin. As illustrated by *Time*, May 15, 1944, “Penicillin will save more lives than war spends.” Penicillin is still an important antibiotic nowadays although resistance has developed. Later on, many other antibiotics were identified. They have been used to treat/prevent various bacterial infections, and have also been included in the therapeutic regimen of surgeries and serious diseases; these dramatically improve the health quality and prolong the life expectancy of human beings. In addition, antibiotics have been supplemented into routine products; for example, adding antibiotics into the fodder and/or drinking water of livestock can prevent diseases, reduce cost and increase productivity.

Antibiotics target structures that are essential for bacterial survival, but unique in bacteria or sufficiently different between bacterial and eukaryotic cells; examples include cell wall, cell membrane, bacterial ribosome, *etc*. Penicillin-like antibiotics have ring-like molecular structures, known as β-lactams. They function by inhibiting the formation of peptidoglycan cross-links in the bacterial cell wall. Bacteria can be resistant to antibiotics by target modification, drug efflux, genetic mutation and enzyme-mediated inactivation. The first strains of penicillin-resistant *S. aureus*, which appeared within a few years of penicillin discovery, were strains that have a survival advantage because they naturally produce an enzyme—penicillinase, a member of β-lactamase family that opens the ring structure of penicillin. Actually, as antibiotics are primarily isolated from microorganisms, such as fungi, most drug resistant genes have their natural resources. Some microorganisms that secrete antibiotics contain resistant genes; some resistant genes are part of normal bacterial biology rather than targeting antibiotics, such

as the drug efflux system; some bacteria acquire resistance after point mutation during evolution. Multi-drug resistance genes have been found in a lot of non-pathogenic environmental bacteria, indicating that microbes have evolved to adapt to the biologic circumstance and they can be a reservoir for multi-drug resistance elements. Resistance in a bacterium can be transferred vertically to its progeny through genetic inheritance and horizontally to other bacterial species through mobile genetic elements, such as transposon, integron and plasmid, which may carry multiple resistant genes, have high mobility and can be easily transmitted to other bacteria. Indeed, genes that cause resistance in pathogens are homologous to those in environmental bacteria, further proving the occurrence and significance of horizontal gene transfer.

"Superbug" is not a new word to describe bacteria that are resistant to more than one type of antibiotics. Many multi-drug resistant (MDR) strains have been identified during the past decades, including methicillin-resistant *Staphylococcus* (MRSA), multi-drug resistant *Tubercles bacillus* (MDR-TB), multi-drug resistant *Streptococcus pneumoniae* (MDRSP), vancomycin-resistant *Enterococcus* (VRE) (Sun et al., 2010). As more and more diseases were cured by antibiotics, the resistant strains were selected to escape from the killing and their survival brought new challenges to antibiotics. This problem potentially got worse due to the widely application of antibiotics in clinic and in routine life. For example, penicillin used to be the most efficient antibiotics half a century ago, but currently, for the same infection, the same efficacy can be hardly accomplished by even tens of folds higher dosage of penicillin. Under the strong pressure of antibiotics, bacteria tend to have more DNA mutations, which potentially generate drug-resistant genes. This hypothesis is supported by the fact that antibiotic resistance was barely detected in the pathogenic bacteria collected before antibiotic generation (Wright, 2010). We are getting into a vicious circle of "antibiotic-resistance-new antibiotic-multi-drug resistance." It seems that the rate of getting new antibiotics cannot meet the rate of bacterial evolution.

Currently, NDM-1 bacteria are only responsive to a small number of drugs, such as tigecycline and colistin, while the efficacy is limited and the toxicity has to be considered. It is accepted that antibiotics resistance is inevitable, but antibiotics abuse is a major accelerator for superbug generation. The reintroduction of plasmid-encoded antibiotic resistant determinants in natural reservoir, together with the selection pressure from human activities, might be relevant to the future evolution and dissemination of antimicrobial resistant determinants in bacterial pathogens (Martínez, 2008). Rules to limit the use of antibiotics, especially for non-therapeutic farming purposes, have been announced by European Union, North America, *etc*. Although the NDM-1 strains are mainly prevalent within hospitals, suggesting their relatively weaker pathogenicity, these superbugs have set the warning alarm to human being for the concerns of future safety. Our next move has to include the careful use of antibiotics in both clinical and agricultural application to win the game with bacterial pathogens.

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