Exploring The World of Antibiotic Resistance

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ANTIBIOTIC RESISTANCE IS BECOMING A PRESSING ISSUE IN THE HEALTHCARE SYSTEM, AS MULTIDRUG RESISTANT BACTERIA ARE RESULTING IN MORE AND MORE DEATHS. WITH VARIOUS MECHANISMS, SUCH AS EFFLUX PUMPS AND ANTIBIOTIC-MODIFYING ENZYMES, MANY BACTERIAL STRAINS ARE ADAPTING TO THE EFFECTS OF ANTIBIOTICS. WITH THE OBSTACLES AND ETHICS FACING NEW DRUG DISCOVERIES IT IS DIFFICULT TO DEVELOP NEW ANTIBIOTICS. HOWEVER, REGULATED PRESCRIPTIONS AND THE UNDERSTANDING OF RESISTANCE BACTERIAL GENES ASSIST IN THE HANDLING AND UNDERSTANDING OF ANTIBIOTIC RESISTANCE. THE FOLLOWING ARTICLE WILL PRESENT VARIOUS ANTIBIOTIC MECHANISMS, ETHICAL ISSUES, AND THE FUTURE OF DRUG RESISTANCE.

Antibiotic resistance is one of the biggest challenges faced by the healthcare sector. In particular, multidrug resistance has posed problems in clinical settings. Many species of bacteria now exhibit multidrug resistance, including *Staphylococcus aureus, Enterococcus faecium and Mycobacterium tuberculosis* (Wright & Sutherland, 2007).

Recent studies have shown that more people in the United States are dying from *methicillin-resistant S. aureus* (MRSA) than from AIDS. According to a report published in The Journal of the American Medical Association, more than 18,000 deaths in U.S. have been attributed to MRSA infections (Boyles, 2005). Discovery of new antibiotics and new therapeutic strategies are essential to help combat this challenge. This article reviews the common resistance mechanisms and evolution of resistance genes while also focusing on recent progress in the development of new strategies for battling antibiotic resistance.

MECHANISMS OF ANTIBIOTIC RESISTANCE

Bacteria have developed numerous strategies to cope with antibiotics. For instance, some bacteria can survive antibiotic treatment by activating resistance mechanisms. The major mechanisms include active efflux of the antibiotic from the cell, transformation of the compound by specific enzymes and prevention of drug interaction through modification of its interaction site.

Pumping Out the Antibiotic

Efflux pumps are transport proteins that can provide innate resistance to antibiotics by expelling toxic substances into the extracellular environment. These proteins can be associated with multiple drug resistance as they often transport antibiotics of distinct structural classes (Webber & Piddock, 2003).

A large proportion of transport genes found in bacteria encode for efflux pumps. Their expression can be part of an operon system, a genetic regulatory system found primarily in prokaryotes. These pumps alone may not be responsible for multiple drug resistance. Regardless, their elevated level of expression in highly resistant clinical strains should not be ignored (Webber & Piddock, 2003). For example, resistance to bile salts and some antibiotics in
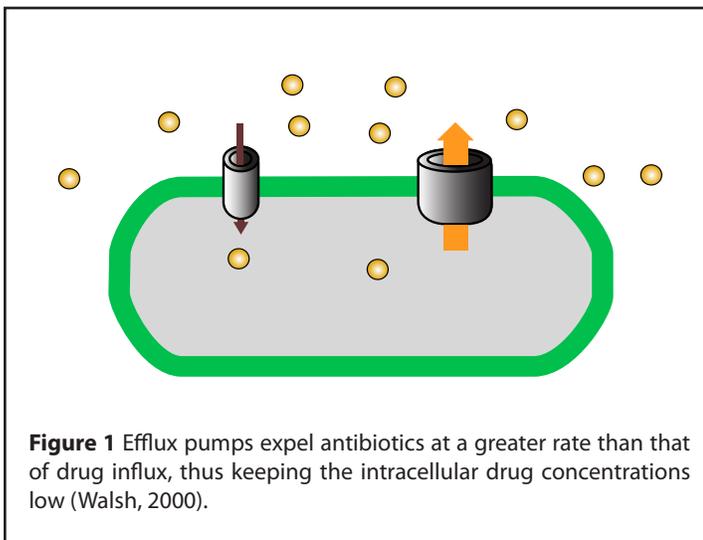
Figure 1 Efflux pumps expel antibiotics at a greater rate than that of drug influx, thus keeping the intracellular drug concentrations low (Walsh, 2000).

A

B
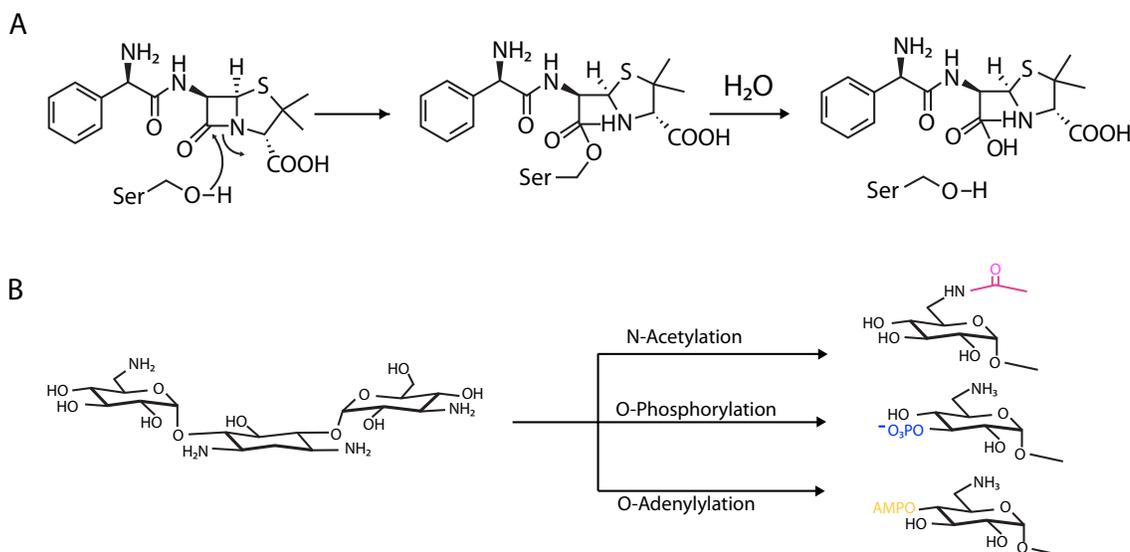
Figure 2 Enzymatic modifications of antibiotics: (a) Hydrolysis of penicillin by Ser-beta-lactamase (Wright, 2005). (b) Modification of kanamycin, an aminoglycoside drug at three different sites is catalyzed by three specific enzymes thereby inhibiting its ability to bind to ribosome (Walsh, 2000).

Escherichia coli has been associated with overexpression of acrAB, an energy dependent efflux mechanism found in the bacteria (Thanassi, Cheng & Nikaido, 1997).

Enzymatic Modifications

Antibiotic-modifying enzymes inactivate antibiotics by chemically altering their structure. This mode of resistance is very specific in comparison to other mechanisms. A classic example is the hydrolysis of the beta-lactam ring by beta-lactamases in penicillin and cephalosporin (Wright, 2005). Another predominant example is the resistance to aminoglycoside drugs brought about by enzymatic inactivation of drug activity. Such enzymes can acetylate the amino group of an antibiotic, preventing the addition of other chemical ligands (Walsh, 2000).

Modification of the Antibiotic Target

This mode of antibiotic resistance can occur through mutations, altering key binding elements, such as ribosomal RNA, or by reprogramming the target (Wright, 2005). For example, a mutation in the penicillin binding protein (PBP) can lower the affinity of penicillin towards PBPs, conferring bacterial resistance to beta-lactam antibiotics. Similar mechanisms have been observed in erythromycin resistance pathways (Walsh, 2000).

EVOLUTION OF ANTIBIOTIC RESISTANCE

Understanding the evolution of resistance and its dissemination within a population can provide valuable insights into solutions for drug resistance (Wright, 2007). It is important to consider the origin of the resistance. Some bacterial species exhibit intrinsic resistance; they remain unaffected without any previous exposure to an antibiotic or without further genetic modifications. Therefore, resistance proteins may have evolved as a result of selective pressures (Wright, 2007).

Bacteria can also pass on resistance genes through horizontal gene transfer. Some of the resistance genes are located on plasmids that replicate independently of the chromosomal DNA. These plasmids can be passed onto other bacterial species as well as between bacterial cells (Wright, 2007).

Mutations resulting in antibiotic resistance can have a fitness cost for an organism in the absence of antibiotics. Mutations may cause alterations in the genetic make up and affect the natural functions of proteins. This may have implications for the survival and fitness of that species (Bjorkholm et al., 2001). Therefore, effective mutations must produce alterations that minimize the interaction of a protein with an antibiotic, while preserving its natural function. A bacterial strain with no fitness cost will have the same likelihood of survival as a bacterial strain that is not under antibiotic selective pressure (Wright, 2007).

It has been shown that resistance comes at a cost of decreased growth rate among other detrimental effects. Therefore, evolution of compensatory mechanisms may be important in stabilizing the resistant bacterial populations. Compensatory mechanisms become extremely important in the context of resistance mutations. A compensatory mechanism may result from another mutation that affects the active site of a protein such that it works as efficiently as the wild type protein (Bjorkholm et al., 2001).

FUTURE DIRECTIONS

The discussion so far alludes to the fact that there is a continuous need for the discovery of new antibiotics. Bacteria are rapidly evolving organisms that utilize strategies to minimize the effect of antibiotics. There are few antibacterial agents against which bacteria have not developed resistance.

Identification of new antibiotics presents a challenge to the drug discovery sector because it is difficult to identify new compounds with antibacterial activity. There has been a significant decline in the rate of identification of new antibacterial compounds since the 1970s. For instance, isolation of new antibiotics from soil has become more difficult as many soil bacteria produce similar range of antibiotics (Wright, 2007).

Recent advancements in the field of bacterial genomics can aid in the discovery of new bacterial targets. A genome provides useful insights into the organization of gene clusters and their regulation (Wright & Sutherland, 2007). Gene disruption methods and chemical libraries used for testing inhibitors offer promise in the expanding field of target site recognition of antibiotics. This could help gain information on target compound pairs that can be exploited in drug designs (Wright & Sutherland, 2007).

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ETHICAL IMPLICATIONS OF ANTIBIOTIC RESISTANCE

Antibiotic resistance challenges our current health care system. There is an urgent need to discover new drugs, but drug discovery proves difficult. One of the biggest challenges faced by drug developing companies is the production and testing of these new products in clinical trials. More importantly, regarding the clinical use of antibiotics, physicians have to decide between the risk of using antibiotic therapy and the well-being of a patient (Garau, 2008). The problem is far more complicated than it appears, and the mindful antibiotic prescription may be a method for reducing the development of antibiotic resistance.

CONCLUDING REMARKS

In the last couple of years, antibiotic resistance, especially multiple drug resistance, has appeared as one of the most significant challenges in the management of infectious diseases. The Infectious Disease Society has identified many problematic pathogens (Talbot et al.,2006). In the near future, it can be expected that this list will grow. Increasing our understanding of the genomics, origin and evolution of resistance genes and mechanisms of resistance can help us to develop new antibiotics and solve the problem of antibiotic resistance. M
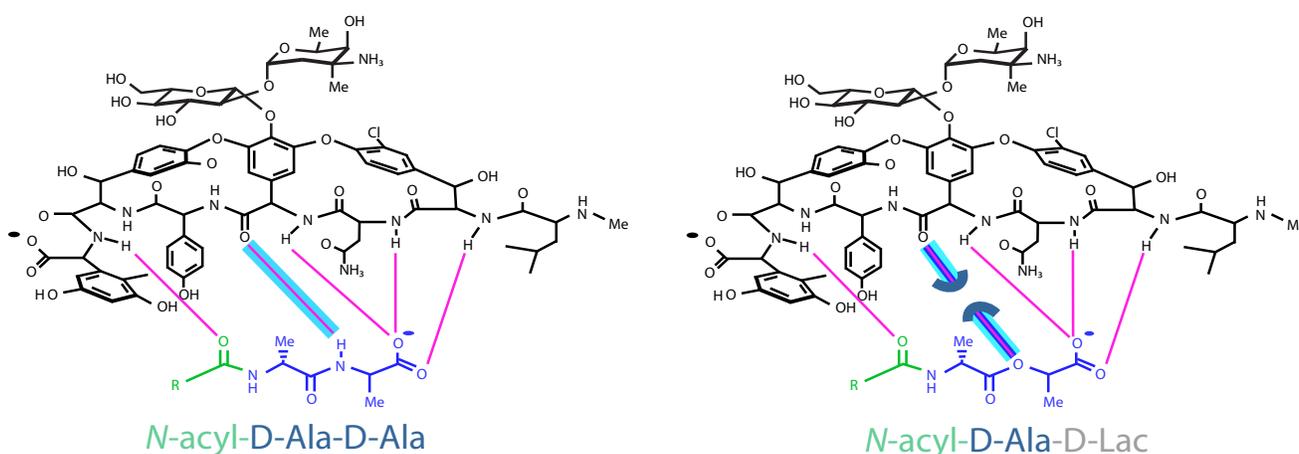
Figure 3 Reprogramming of the target structure in a bacterium: replacement of an amide linkage with an ester linkage causes a 1000-fold drop in the binding affinity of the drug vancomycin for the bacterial cell wall (Walsh, 2000).

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