Mechanisms of antimicrobial resistance

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Abstract

The consequences of bacterial infections have been curtailed by the introduction of a wide range of antibiotics. However, infections continue to be a leading cause of mortality, in part due to the evolution and acquisition of antibiotic-resistance genes. Antibiotic misuse and over prescription have created a driving force influencing the selection of resistance. Despite the problem of antibiotic resistance in infectious bacteria, little is known about the diversity, distribution and origins of resistance genes, especially for the unculturable majority of environmental bacteria. Functional and sequence-based metagenomics have been used for the discovery of novel resistance determinants and the improved understanding of antibiotic-resistance mechanisms in clinical and natural environments. This review discusses recent findings and future challenges in the study of antibiotic resistance through metagenomic approaches

Introduction

Infectious diseases are the second-leading cause of death globally and the most significant cause of death in children. Antibiotics represent one of the largest therapeutic categories used in the treatment of infectious diseases caused by bacteria, but the successful use of any therapeutic agent is compromised by the potential development of tolerance or resistance to that compound from the time it is first employed. In clinical environments, pathogenic and commensal bacteria are challenged with high concentrations of antibiotics and bacteria have become resistant to most of the antibiotics developed.

Antibiotic resistance mechanisms

1. To stop the antibiotic from reaching its target bacteria may:

➢ ***Pump the antibiotic out from the bacteria*:**

Bacteria can produce pumps that sit in their membrane or cell wall. These so-called efflux pumps are very common in bacteria and can transport a variety of compounds such as signal molecules and nutrients. Some of these pumps can also transport antibiotics out from the bacterium, in this way lowering the antibiotic concentration inside the bacterial cell. In some cases mutations in the bacterial DNA can make the bacteria produce more of a certain pump, which in turn increases resistance.

➢ ***Decrease permeability of the membrane that surrounds the bacterial cell*:**

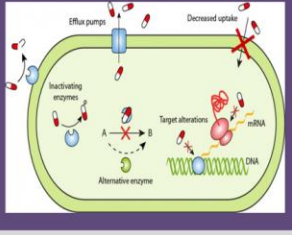
Certain changes in the bacterial membrane make it more difficult to pass through. In this way, less of the antibiotic gets into the bacteria.

➢ ***Destroy the antibiotic*:**

There are bacterial enzymes that can inactivate antibiotics. One example is β-lactamase that destroys the active component (the β-lactam ring) of penicillin, extremely important antibiotics for treating human infections. In later years, bacteria that produce extended-spectrum β-lactamases, so called ESBL-producing bacteria, have become a major problem. They can degrade a wide spectrum of β-lactam antibiotics, sometimes also the last resort drugs available for infections with these bacteria.

➢ ***Modify the antibiotic*:**

Bacteria can sometimes produce enzymes that are capable of adding different chemical groups to antibiotics. This in turn prohibits binding between the antibiotic and its target in the bacterial cell.



2. To modify or bypass the target that the antibiotic inhibits bacteria can:

➢ ***Camouflage the target*:**

Changes in the composition or structure of the target in the bacterium (resulting from mutations in the bacterial DNA) can stop the antibiotic from interacting with the target. Alternatively, the bacteria can add different chemical groups to the target structure, in this way shielding it from the antibiotic.

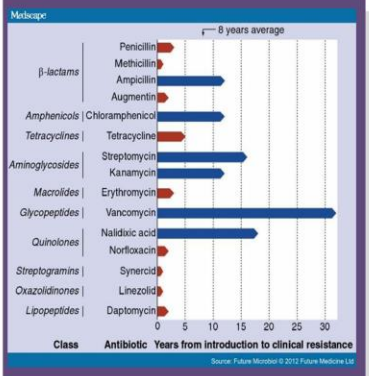
➢ ***Express alternative proteins*:**

Some bacteria are able to produce alternative proteins that can be used instead of the ones that are inhibited by the antibiotic. For example, the bacterium *Staphylococcus aureus* can acquire the resistance gene *mecA*and produce a new penicillin-binding protein. These proteins are needed for bacterial cell wall synthesis and are the targets of β-lactam antibiotics. The new penicillin-binding protein has low affinity to β-lactam antibiotics and is thus resistant to the drugs, and the bacteria survive treatment. This type of resistance is the basis in MRSA (methicillin-resistant *Staphylococcus aureus*).

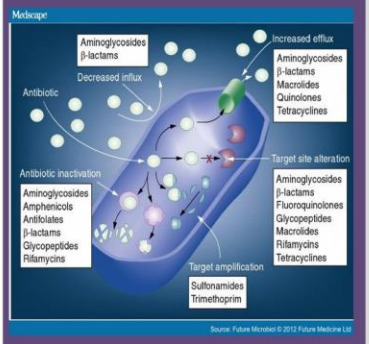
➢ ***Reprogram target*:**

Sometimes bacteria can produce a different variant of a structure it needs. For example, Vancomycin-resistant bacteria make a different cell wall compared to susceptible bacteria. The antibiotic is not able to interact as well with this type of cell wall.

Some bacteria are naturally resistant to certain antibiotics. Imagine for example an antibiotic that destroys the cell wall of the bacteria. If a bacterium does not have a cell wall, the antibiotic will have no effect. This phenomenon is called intrinsic resistance. When a bacterium that was previously susceptible to an antibiotic evolves resistance it is called acquired resistance.



Antibiotic resistance evolution showing the rapid development of resistance for several classes of antibiotics.



Mechanisms of antibiotic resistance in bacteria. The classes of antibiotics affected by each of the mechanisms are listed in the boxes

Conclusion

We are dependent on antibiotics for the treatment of infectious diseases and they are critical for the success of advanced surgical procedures, such as organ and prosthetic transplants. Antibiotic-resistance mechanisms create an enormous clinical and financial burden on healthcare systems worldwide. Despite the problem of antibiotic resistance in infectious bacteria, little is known about the diversity, distribution and origins of resistance genes, especially for the unculturable majority of environmental bacteria.

Reference

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