

Bacterial Resistance to Antibiotics (page 3)

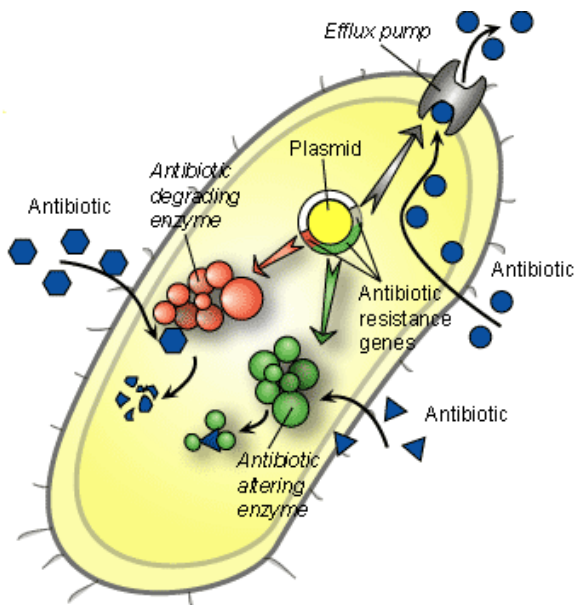
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Bacterial mechanisms of antibiotic resistance

Several mechanisms have evolved in bacteria which confer them with antibiotic resistance. These mechanisms can either chemically modify the antibiotic, render it inactive through physical removal from the cell, or modify target site so that it is not recognized by the antibiotic.

The most common mode is enzymatic inactivation of the antibiotic. An existing cellular enzyme is modified to react with the antibiotic in such a way that it no longer affects the microorganism. An alternative strategy utilized by many bacteria is the alteration of the antibiotic target site. These and other mechanisms are shown in the the figure and accompanying table below.



Three mechanisms of antibiotic resistance in bacteria. Most, but not all, resistance mechanisms are encoded by plasmids, which are potentially transmissible to other bacteria. Clockwise. 12 o'clock: Efflux pumps are high-affinity reverse transport systems located in the membrane that transport the antibiotic out of the cell. This is the mechanism of resistance to tetracycline. 4 o'clock: A specific enzyme modifies the antibiotic in a way that it loses its activity. In the case of streptomycin, the antibiotic is chemically modified so that it will no longer bind to the ribosome to block protein synthesis. 9 o'clock: An enzyme is produced that degrades the antibiotic, thereby inactivating it. For example, the penicillinases are a group of beta-lactamase enzymes that cleave the beta lactam ring of the penicillin molecule.

Antibiotic

Method of resistance

| | |
|--|---|
| Chloramphenicol | reduced uptake into cell |
| Tetracycline | active efflux from the cell |
| β -lactams, Erythromycin, Lincomycin | eliminates or reduces binding of antibiotic to cell target |
| β -lactams, Aminoglycosides, Chloramphenicol | enzymatic cleavage or modification to inactivate antibiotic molecule |
| Sulfonamides, Trimethoprim | metabolic bypass of inhibited reaction |
| Sulfonamides, Trimethoprim | overproduction of antibiotic target (titration) |

The acquisition and spread of antibiotic resistance in bacteria

The development of resistance is inevitable following the introduction of a new antibiotic. Initial rates of resistance to new drugs are normally on the order of 1%. However, modern uses of antibiotics have caused a huge increase in the number of resistant bacteria. In fact, within 8-12 years after wide-spread use, strains resistant to multiple drugs become widespread. Multiple drug resistant strains of some bacteria have reached the proportion that virtually no antibiotics are available for treatment.

Antibiotic resistance in bacteria may be an inherent trait of the organism (e.g. a particular type of cell wall structure) that renders it **naturally resistant**, or it may be **acquired** by means of mutation in its own DNA or acquisition of resistance-conferring DNA from another source.

Inherent (natural) resistance. Bacteria may be inherently resistant to an antibiotic. For example, an organism lacks a transport system for an antibiotic; or an organism lacks the target of the antibiotic molecule; or, as in the case of Gram-negative bacteria, the cell wall is covered with an outer membrane that establishes a permeability barrier against the antibiotic.

Acquired resistance. Several mechanisms are developed by bacteria in order to acquire resistance to antibiotics. All require either the modification of existing genetic material or the acquisition of new genetic material from another source.

Vertical gene transfer

The spontaneous mutation frequency for antibiotic resistance is on the order of about 10^{-8} - 10^{-9} . This means that one in every every 10^8 - 10^9 bacteria in an infection will develop resistance through the process of mutation. In *E. coli*, it has been estimated that streptomycin resistance is acquired at a rate of approximately 10^{-9} when exposed to high concentrations of streptomycin. Although mutation is a very rare event, the very fast growth rate of bacteria and the absolute number of cells attained means that it doesn't take long before resistance is developed in a population.

Once the resistance genes have developed, they are transferred directly to all the bacteria's progeny during DNA replication. This is known as **vertical gene transfer**

or **vertical evolution**. The process is strictly a matter of Darwinian evolution driven by principles of natural selection: a spontaneous mutation in the bacterial chromosome imparts resistance to a member of the bacterial population. In the selective environment of the antibiotic, the wild type (non mutants) are killed and the resistant mutant is allowed to grow and flourish

Horizontal gene transfer

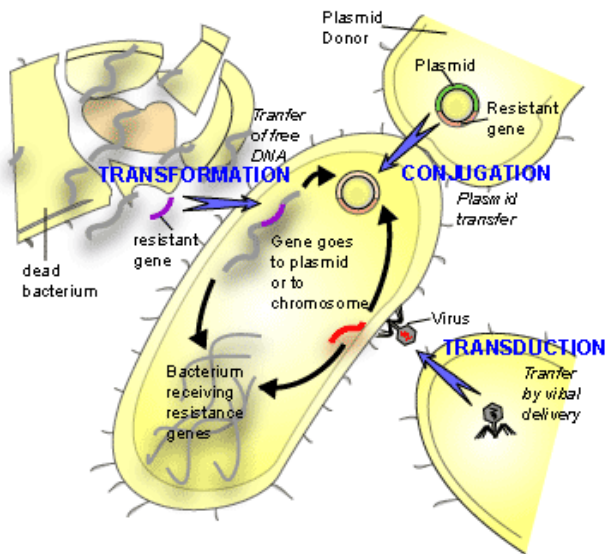
Another mechanism beyond spontaneous mutation is responsible for the acquisition of antibiotic resistance. Lateral or **horizontal gene transfer** (HGT) is a process whereby genetic material contained in small packets of DNA can be transferred between individual bacteria of the same species or even between different species.

There are at least three possible mechanisms of HGT, equivalent to the three processes of genetic exchange in bacteria. These are transduction, transformation or conjugation.

Conjugation occurs when there is direct cell-cell contact between two bacteria (which need not be closely related) and transfer of small pieces of DNA called plasmids takes place. This is thought to be the main mechanism of HGT.

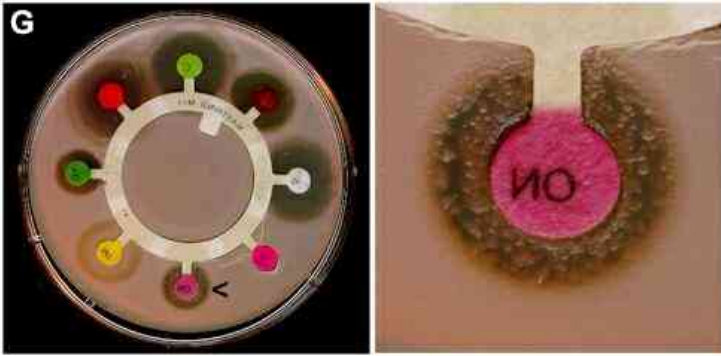
Transformation is a process where parts of DNA are taken up by the bacteria from the external environment. This DNA is normally present in the external environment due to the death and lysis of another bacterium.

Transduction occurs when bacteria-specific viruses (bacteriophages) transfer DNA between two closely related bacteria.



Mechanisms of horizontal gene transfer (HGT) in bacteria

The combined effects of fast growth rates to large densities of cells, genetic processes of mutation and selection, and the ability to exchange genes, account for the extraordinary rates of adaptation and evolution that can be observed in the bacteria. For these reasons bacterial adaptation (resistance) to the antibiotic environment seems to take place very rapidly in evolutionary time. Bacteria evolve fast!



Tests for sensitivity and resistance to antibiotics. (Left) The size of the zones of inhibition of microbial growth surrounding the antibiotic disks on the plate are an indication of microbial susceptibility to the antibiotic. (Right) By the use of these disks it is also possible to detect the occurrence of individual mutants within the culture that have developed antibiotic resistance. This image shows a close-up of the novobiocin disk (marked by an arrow on the whole plate) near which individual mutant cells in the bacterial population that were resistant to the antibiotic and have given rise to small colonies within the zone of inhibition.

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