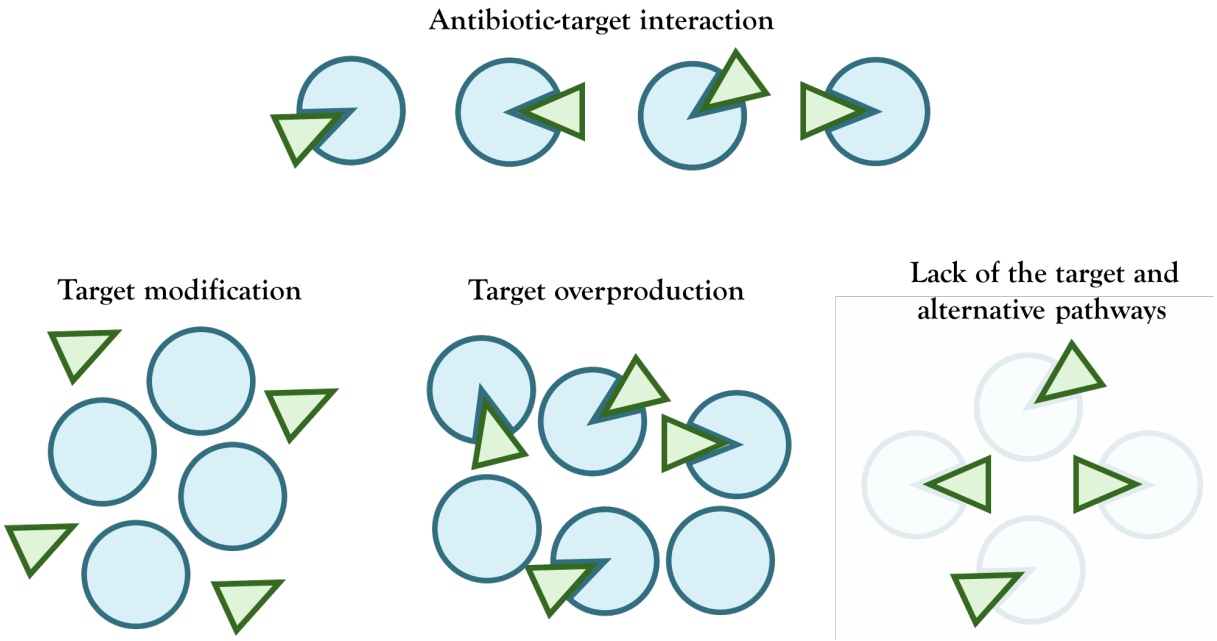
Antimicrobial Resistance Gallery

Resistance mechanisms: target modification

(Teresa Gil-Gil)



Imagine bacteria as tiny creatures with a protective wall around them. Antibiotics need to get through this wall, in some cases be activated, and reach their targets to inhibit bacterial growth. Hence, activity of the antibiotic depends on its capacity to bind its target. This interaction is highly specific, like a lock (the target) and key (the antibiotic). When the key fits the lock, the bacteria become inhibited and can no longer cause harm to us. However, bacteria can change the antibiotic target – the lock – so that the antibiotic no longer fits and does its job, and thereby become resistant to the antibiotic – the key.

An example of target-related resistance mechanisms is mutations in the target, which prevent binding of the antibiotic. For example, mutations in the RNA polymerase can confer resistance to rifampicin, while mutations in genes encoding the GyrA, GyrB, ParC, and ParE proteins confer resistance to fluoroquinolones, and mutations in the genes encoding the ribosome 30S subunit proteins RpsU, RpsJ, and RpsA make bacteria resistant to tigecycline. All these proteins are targets for antibiotics that inhibit expression of the generic information of the bacteria. Similarly, genetic mutations in proteins like penicillin-binding proteins, which are targets for beta-lactam antibiotics, reduce their binding affinity to antibiotics, preventing effective binding and leading to acquired resistance. Penicillin-binding proteins play a major role in creating a stable bacterial cell wall, so inhibiting them weakens the wall and kills the bacteria.

In some cases, bacteria inherently lack the specific target or possess a naturally resistant variant of the target. For instance, certain pathogens like *Chlamydia*, which can cause sexually-transmitted infections, or *Borrelia burgdorferi*, which causes Lyme disease, have MurA enzyme variants that lack a critical cysteine, making them intrinsically resistant to the antibiotic fosfomycin.

Another target resistance mechanism is the production of enzymes that chemically modify the target to make it insensitive to certain antibiotics. This can include methylation of an adenine in the 23S rRNA, rendering it insensitive to macrolides, or the reorganization of the cell wall making it resistant to vancomycin.

Bacteria can also develop resistance by replacing the target itself, acquiring modified proteins or using alternative pathways. Changing the design of the beta-lactams targets present in the cell wall (penicillin-binding proteins), or opting for a different approach, where instead of rebuilding the wall all over again each time (utilizing the fosfomycin target enzyme, MurA), the bacteria recycle components of the wall through an alternative route to develop resistance.

Then there exist target protective measures, such as the production of proteins like Qnr (protecting bacterial topoisomerases from the inhibitory activity of quinolones), which can shield essential bacterial enzymes from the inhibitory effects of antibiotics.

Target overproduction is another resistance mechanism where bacteria produce more of the target protein. In this case, the antibiotic still binds to and inhibits the target, but the amount of antibiotic entering the cells is insufficient to inhibit all target molecules, so bacterial growth is not effectively inhibited. Mutations in regulators that enhance the transcription of genes coding for certain targets is a common means of target overproduction, an example of which is the increased expression of the fosfomycin target, MurA.

Microbes thus have several options to stop antibiotics from binding to and inactivating their targets within the cell, thereby making these microbes antibiotic resistant. A better understanding of these mechanisms is crucial to developing new strategies to combat antibiotic resistance.