

mechanisms of antimicrobial resistance
[created by Paul Young 02/10/07]

natural resistance

- Some organisms are naturally resistant to a particular antimicrobial agent, usually because they do not possess the molecular target of the drug or are impermeable to it.

acquired resistance

- Acquired resistance occurs through mutation or the acquisition of new genetic material carried by mobile elements such as plasmids and transposons.
- Multiple pathways allow free exchange of genetic material within and across microbial species and even genera.
- The four major mechanisms for acquired resistance are:
(i) drug inactivation,
(ii) target modification,
(iii) reduced permeability and
(iv) drug efflux pumps.
- These mechanisms often act synergistically to produce a resistant phenotype when a single mechanism alone would not be sufficient.
- Moreover, selective pressure may result in the 'bundling' together of several resistance genes in a single package of exchangeable genetic material. This is particularly common in highly resistant Gram-negative organisms.

Examples:

(i) beta-lactamases
- Beta-lactamases are enzymes that hydrolyse the betalactam ring.
- Penicillin contains such a ring and is therefore inactivated by these enzymes. The first betalactamase was discovered in *S. aureus*
- Gram-negative organisms naturally produce a wide range of beta-lactamases; some are chromosomally encoded and others reside on plasmids. The first plasmid-mediated betalactamase, TEM-1, was originally isolated in *Escherichia coli* in the 1960s and within a few years had spread to many species of Enterobacteriaceae and *Pseudomonas* spp. This beta-lactamase is active against all penicillins but not against cephalosporins
(ii) extended spectrum beta lactamases
- Through amino acid substitutions, the spectrum of enzymatic activity has increased to include broad-spectrum third generation cephalosporins. These enzymes are collectively known as the extended spectrum beta-lactamases.
- Some of these are specific cephalosporinases with some having broader activity, while others possess resistance to beta-lactamase inhibitors

drug inactivation

General:

- This mechanism includes either modification of the antimicrobial target causing reduced affinity for the drug, or replacement of the target with an alternative pathway.

Examples

(i) MRSA and coagulase negative *S. aureus* is principally due to the production of a novel low-affinity penicillin-binding protein (PBP2a)
(ii) Similarly, alterations in penicillin-binding proteins with low affinity for beta-lactams occur in other organisms including Enterococci and Streptococci.
(iii) One of the mechanisms of fluoroquinolone resistance is the alteration of the A subunit of topoisomerase IV by a point mutation in the encoding *grl-A* gene.
(iv) The substitution of an alternative pathway is best illustrated by the vancomycin-resistance Enterococci, where a new substrate for cell wall synthesis (D-alanine D-lactate) is used and this is not affected by vancomycin

target modification

reduced permeability

General:

- Reduced antibiotic permeability of the bacterial cell membrane often acts synergistically with another mechanism such as drug inactivation to produce clinical resistance when neither alone could do so.

Examples:

(i) The relative impermeability of the outer membrane is one of the major causes of the high levels of intrinsic drug resistance seen in opportunistic Gram-negative pathogens like *S. maltophilia* and *P. aeruginosa*.
(ii) Antibiotic movement across the outer membrane occurs through porin channels that allow hydrophilic molecules to cross the lipid bilayer. Thus, loss of the OprD porin in *P. aeruginosa* produces high-level imipenem resistance and a reduced susceptibility to meropenem

drug efflux pumps

General:

- Drug efflux is the energy-dependent removal of drugs from organisms before the drug can act

Examples:

(i) substrate-specific efflux pumps like the widespread macrolide and tetracycline efflux systems
(ii) MexABOprM system which can export a broad range of substrates, producing cross-resistance to a number of structurally unrelated agents. This system has been identified in *P. aeruginosa*, where the MexB protein is a broad-spectrum cytoplasmic pump; the OprM protein forms a pore that provides a portal through the outer membrane and the MexA protein physically links these components. The system confers resistance to penicillins, cephalosporins, fluoroquinolones, tetracycline and chloramphenicol.
(iii) Combination of the MexAB-OprM operon with loss of OprD produces resistance to meropenem in addition to imipenem, although it is not the only efflux mechanism responsible for carbapenem resistance in *P. aeruginosa*
(iv) Multi-drug efflux mechanisms have been identified in other organisms including Enterobacteriaceae. Mutation of a chromosomal locus termed *mar* (for multiple antibiotic resistance), which regulates susceptibility to unrelated antimicrobials, results in a combination of active efflux and down-regulation of the OmpF porin channel