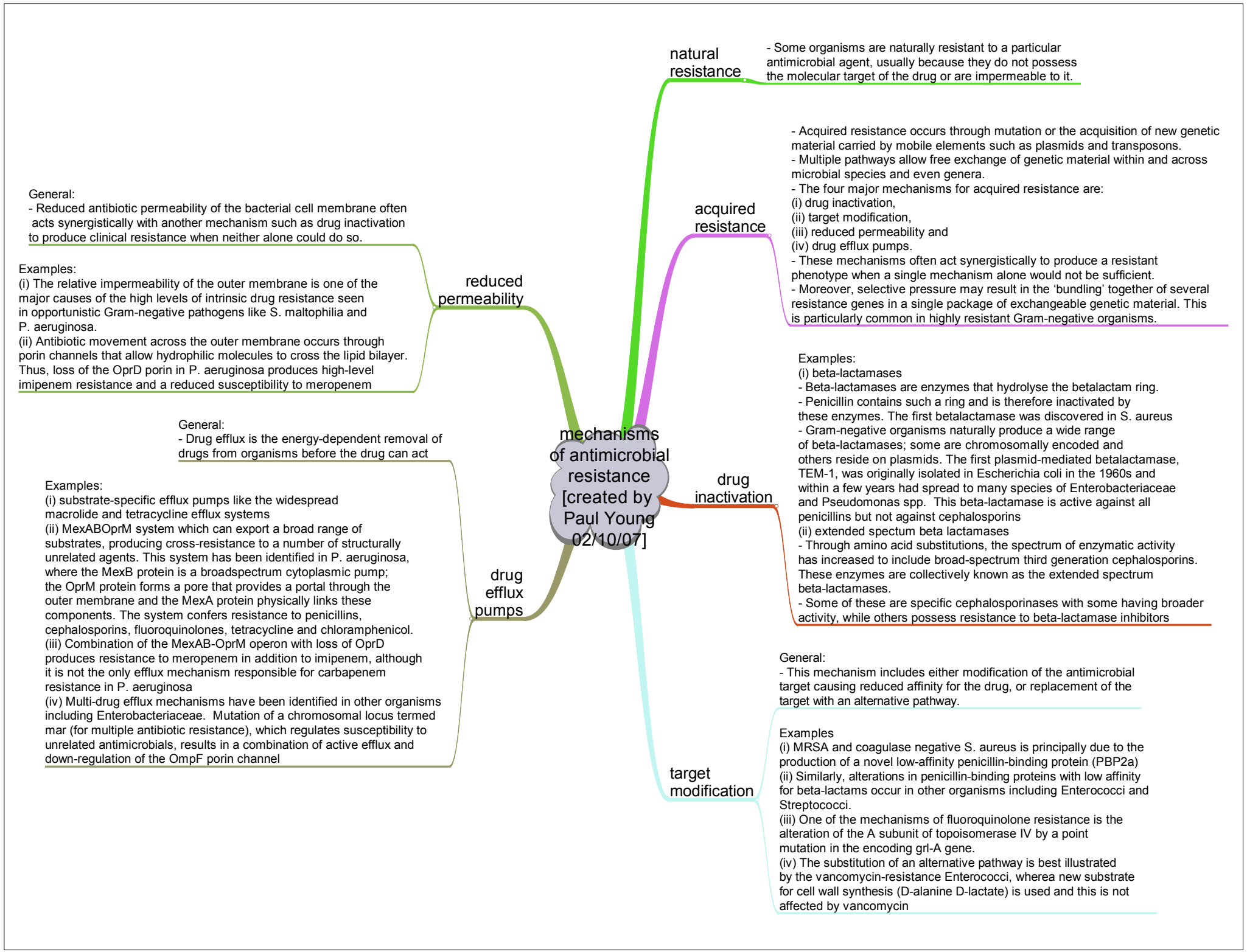
mechanisms of antimicrobial resistance [created by Paul Young 02/10/07]
natural resistance
- Some organisms are naturally resistant to a particular antimicrobial agent, usually because they do not possess the molecular target of the drug or are impermeable to it.
acquired resistance
- Acquired resistance 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.
drug inactivation
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 spectum 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
target modification
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, wherea new substrate for cell wall synthesis (D-alanine D-lactate) is used and this is not affected by vancomycin
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 broadspectrum 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
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