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Antibiotics and resistance

Today is my last lecture- Monday Professor Traxler will begin. The lecture will be short today to leave time for course evaluations. I want to finish my lectures with an overview of the genetics of one of the most important clinical challenges facing us - the widespread occurrence of antibiotic resistance in bacterial pathogens. Evolution of multiply resistant organisms has meant that we are running out of antibiotics to treat some infections. Drug companies aren't very seriously invested in new antibiotic discovery.

Example from a week and a half ago in the news- Brazillian model infected with an antibiotic resistant strain; urinary infection spread into blood and into the soft tissues of hands and feet. Amputated to prevent spread, but too late and she died a few days later.

Outline- discuss three of the most important antibiotic classes. In each cae, discuss targets and resistance, then at the end I'll cover the genetic elements responsible for encoding resistance

Slide- shows three classes of targets- other targets also exist not on here but these are the most important. Ask if anyone knows other targets? RNA polymerase (rif), folate metabolism (sulfanilamide, trimethoprim), fatty acid biosynthesis (triclosan)

PP- gyrase mechanism
- note first structure not supercoiled, has + and – crossings; change to structure at far right with supercoils. Topo IV as second target- both imp, but relative importance depends on bacterial species
- Mention multiple targets as rule for best abts;

PP- gyrase mutations

PP- Damage tolerance- increased mutation rate may stimulate gyrase resistance mutations!

PP efflux; One class with three components; others are simpler transporters with only IM pump, e.g., Tet of Tn10.

PP beta-lactams- point out ring
-multiple penicllin binding proteins. In periplasm!

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No cross-linking; septation step very sensitive; cells lyse
PP- penicillinase (beta-lactamase)- acts in periplasm

PP- Damage tolerance; still being worked out, and a surprise (unlike cipro). Again- SOS induction increasing basal mutation rate!

PP- aminoglycoside mechanism- mention interacts with rRNA in 30S ribosome

Resistance- amazing variety of modifying enzymes

PP- target 16S methylated

PP Genetic elements associated with resistance- go through

PP- Tns

PP- integrons- stress, figure shows evolutionary scenario hypothesized; superintegrons can have more than 100 casettes inserted!

PP- example- Quaternary ammonium salts- biocides used to sterilize surfaces, etc of bacteria. Chlorine bleach is used for same purpose

PP- RI plasmid- resistances, transfer, replication- notice ISs- they can mobilize resistances in transposition

PP- ICEs- still actively being researched and behavior not fully understood
-often carry abt resistance genes; usually transfer. Some don't have transfer genes and may get mobilized by plasmids which do (hitchhiking)