RAMA UNIVERSITY

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FACULTY OF ENGINEERING &TECHNOLOGY

DEPARTMENT OF BIOTECHNOLOGY

Mode of action of antibiotics

Antibacterial action generally falls within one of four mechanisms, three of which involve the inhibition or regulation of enzymes involved in cell wall biosynthesis, nucleic acid metabolism and repair, or protein synthesis, respectively.

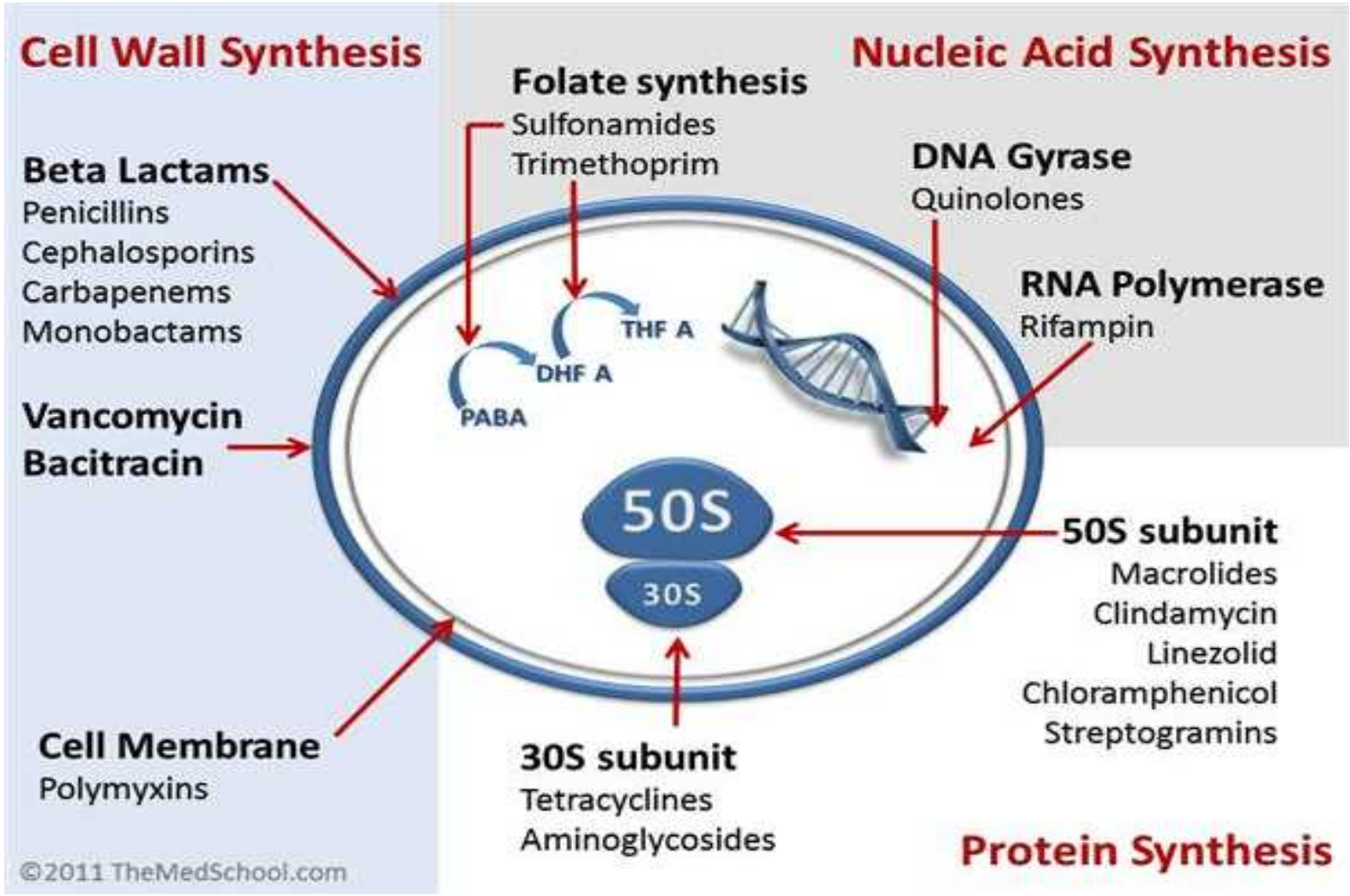
The fourth mechanism involves the disruption of membrane structure.

Many of these cellular functions targeted by antibiotics are most active in multiplying cells.

Since there is often overlap in these functions between prokaryotic bacterial cells and eukaryotic mammalian cells, it is not surprising that some antibiotics have also been found to be useful as anticancer agents.

There are Five Basic Mechanisms of Antibiotic Action against Bacterial Cells:

- Inhibition of Cell Wall Synthesis (most common mechanism)
- Inhibition of Protein Synthesis (Translation) (second largest class)
- Alteration of Cell Membranes
- Inhibition of Nucleic Acid Synthesis
- Antimetabolite Activity


Cell Wall Synthesis
Nucleic Acid Synthesis
Folate synthesis
Sulfonamides
Trimethoprim
Beta Lactams
Penicillins
Cephalosporins
Carbapenems
Monobactams
DNA Gyrase
Quinolones
RNA Polymerase
Rifampin
THF A
DHF A
PABA
Vancomycin
Bacitracin
50S
30S
50S subunit
Macrolides
Clindamycin
Linezolid
Chloramphenicol
Streptogramins
Cell Membrane
Polymyxins
30S subunit
Tetracyclines
Aminoglycosides
Protein Synthesis
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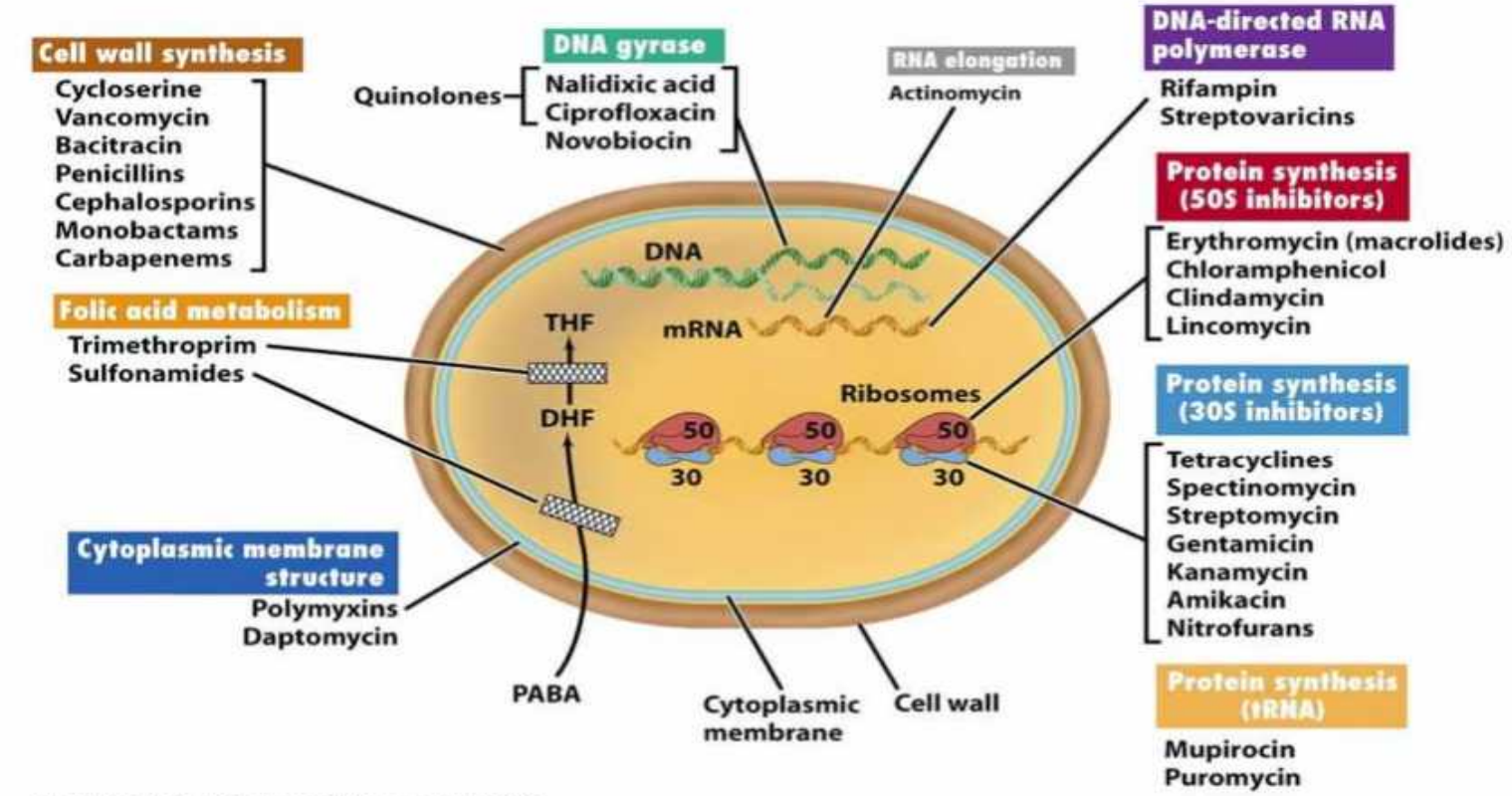

Figure 20-14 Brock Biology of Microorganisms 11/e
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Figure: The above two figures depict the mechanism of action of various antibiotics against bacteria (An important figure for competitive exam point of view).

Sulfa/ Sulfonamide drugs

Sulfonamides or sulfa drugs are synthetic antibacterial drugs structurally related to sulfanilamide, an analogue of *p* aminobenzoic acid. The latter substance is used in the synthesis of the cofactor folic acid.

Mode of action: When sulfanilamide or another sulfonamide enters a bacterial cell, it competes with *p*-aminobenzoic acid for the active site of an enzyme involved in folic acid synthesis, and the folate concentration decreases. The decline in folic acid is detrimental to the bacterium because folic acid is essential to the synthesis of purines and pyrimidines, the bases used in the construction of DNA, RNA, and other important cell constituents. The resulting inhibition of purine and pyrimidine synthesis leads to cessation of bacterial growth or death of the pathogen.

Example of two sulfadrugs: Sulfamethoxazole, and sulfisoaxazole

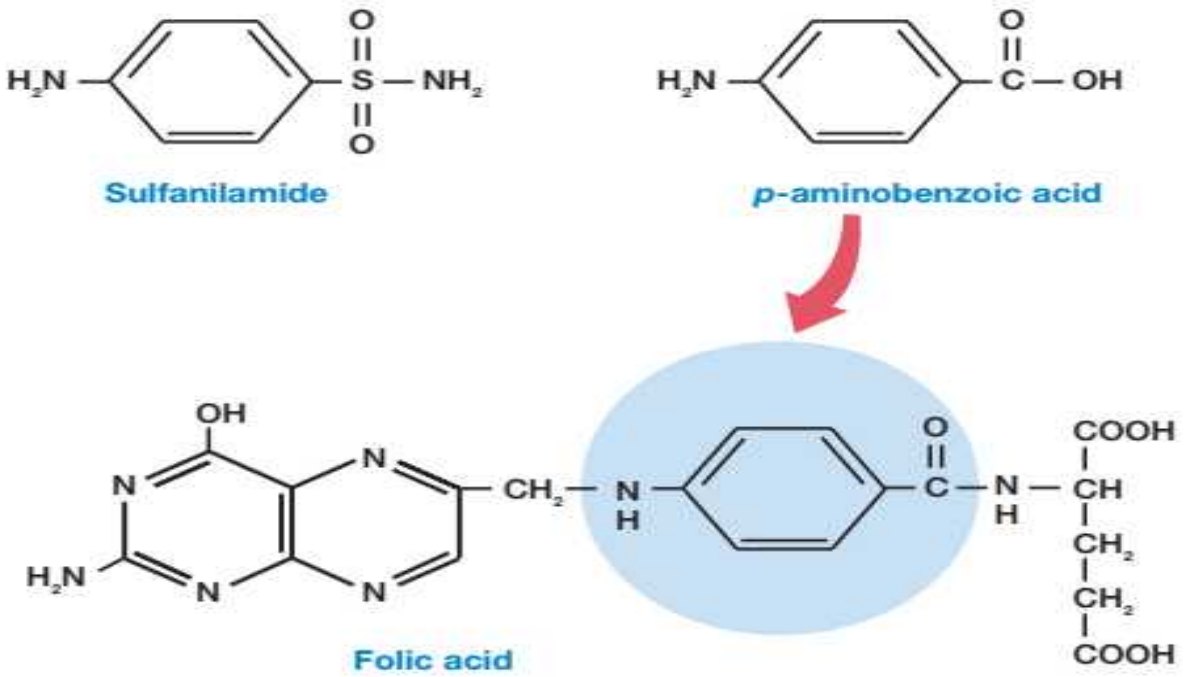

Figure 35.3 Sulfanilamide. Sulfanilamide and its relationship to the structure of folic acid.

Penicillins:

Penicillin G or benzylpenicillin, the first antibiotic to be widely used in medicine. Most **penicillins** are derivatives of 6-aminopenicillanic acid and differ from one another only with respect to the side chain attached to its amino group. The most crucial feature of the molecule is the β-lactam ring, which appears to be essential for activity.

Penicillinase, the enzyme synthesized by many penicillin-resistant bacteria, destroys penicillin activity by hydrolyzing a bond in this ring.

Mode of action:

Bacterial cell walls consist of a protective peptidoglycan layer, which is continuously undergoing remodeling.

The remodelling process involves the breaking of the β-(1,4) linked N-acetylmuramic acid and N-acetylglucosamine; as well as the breaking of the cross-linking peptide chains.

This cross-linking peptide chains is what provides the rigidity, to the otherwise fluid cell wall.

The breaking of this peptide cross-linking is performed by an enzyme called transpeptidase.

The transpeptidase also helps in reforming the peptide bonds once the restructuring of the cell wall is done.

The penicillins act by inhibiting this particular enzyme.

By inhibiting this enzyme the penicillin prevents the reformation of the peptide bonds and thus makes the cell wall less strong.

This loss of cell wall integrity causes the bacteria to leak out its cellular contents and perish.

This beta-lactam ring of the penicillin is generally not very stable and therefore it participates in the inactivation of bacterial cell enzymes which are essential for synthesis of peptidoglycan.

Transpeptidase attacks the beta-lactam ring which opens up to give a more stable compound.

When this happens the drug remains bound to the transpeptidase via covalent linkage and thereby inhibits the enzyme by acylation of the active site.

The mechanism is consistent with the observation that penicillins act only on growing bacteria that are synthesizing new peptidoglycan.

Different types of penicillins: Penicillin G, Penicillin V, Ampicillin, Methicillin, Carbenicillin etc.

Cephalosporin

Cephalosporins are a family of antibiotics originally isolated in 1948 from the fungus *Cephalosporium (also known as Acremonium chrysogenum),* and their β-lactam structure is very similar to that of the penicillins. They are broad-spectrum drugs frequently given to patients with penicillin allergies.

Mode of action:

The killing mechanism is similar to penicillin. cephalosporins bind to the transpeptidase enzyme and block the formation of the peptide cross-links. This results in a weak cell wall and osmotic lysis of the bacterium.

Example of Cephalosporin: Most cephalosporins (including cephalothin, cefoxitin, ceftriaxone, and cefoperazone) are administered parenterally. Cefoperazone is resistant to destruction by β-lactamases and effective against many gram-negative bacteria, including *Pseudomonas aeruginosa.* Cephalexine and cefixime are given orally rather than by injection.