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PHARMACOLOGY

Question :List and explain 4 mechanism of antimicrobial resistance

- ★ Intrinsic resistance
- ★ Mutation
- ★ Inactivation of antibiotics
- ★ Hoizontal gene transfer

1.Intrinsic resistance

Environmental changes, such as radiation, changes in light or pH can all contribute to resistant bacteria and have been reviewed thoroughly However, a consideration must also be given to the internal intrinsic resistance that bacteria naturally possess. Intrinsic resistance usually utilizes enzymes to destroy the drug or prevent intracellular drug binding within the target organism. The innate ability of bacteria to resist antibiotics is known as ‘insensitivity’ as organisms have not been exposed to that drug but still have a level of resistance

2.Mutation

Since the mid-20th century, multidrug-resistant pathogens have had a clinical relevance, and can be attributed to mutations in the bacteria themselves. Recently, with the improvement of molecular techniques, mutations have become more apparent and easier to detect.

Random point mutations can occur in any species and have recently been documented in Helicobacter pylori Mutations within the 23 s rRNA are of particular interest as within it lies the most common binding site for antibiotics to inhibit transcription and translation. Clarithromycin resistance or mutations in the 23 s rRNA gene of H. Pylori may prevent the treatment of pneumonia and skin infections . Interestingly, mutations in the 23 s rRNA in Staphylococcal species are associated with reduced susceptibility to linezolid. Extensive clinical use of linezolid has led to resistance selection in S. aureus and Streptococus pneumoniae; however, it is still

effective in >98% of Staphylococcus species

3.Inactivation of antibiotics

Bacterial enzymes have been shown to add chemical groups to vulnerable sites on the antibiotic molecule preventing the antibiotic from binding to its original target . Within the structure of an antibiotic, hydroxyl and amides groups can easily be changed by hydrolysis . Moreover, acetyl, phosphate and nucleotide groups can be added to the antibiotics inactivating them

Staphylococcus aureus has shown resistance to penicillin which is mediated by the blaZ gene that codes for β-lactamase . β-lactam antibiotics inhibit the biosynthesis of the bacterial cell wall by preventing the cross links which form the wall, and weaken it leaving bacteria unable to proliferate The β-lactamase enzyme is synthesized when Staphylococci are exposed to β-lactam antibiotics and hydrolyses the ring leaving the antibiotic inactivated and unable to destroy the bacteria

4.Horizontal gene transfer

For microbial species to maintain resistance to antibiotics, they must not only pass resistance genes to their progeny but also have the ability to transfer genes between species, known as horizontal gene transfer . There are three types of horizontal gene transfer which include: the AMR gene being associated with mobile genetic elements such as mobile introns; loss of synteny (genetic loci) of the insertion site in the host; and acquiring an AMR gene through gene transfer Multiple copies of resistant genes give bacteria the best possible chance to avoid antibiotics. An example can be found in Gram-positive bacteria to provide linezolid resistance, where there are six copies of the gene 23 s rRNA which play an important role in AMR However, this has the metabolic burden of producing extra proteinsVonwintersdorff et al. recently reviewed horizontal gene transfer more thoroughly

In addition to the mobile genetic elements, the integrons, a type of transposon, can be transferred to other bacteria allowing bacteria to evolve due to the acquisition of new genes. Theoretically, DNA can be randomly inserted onto the nonhomologous end of a DNA sequence; however, the likelihood and frequency of this is extremely low. Natural transformation may also occur with AMR genes integrated into the bacterial genome In their paper they also explored the transfer of proteobacterial genes, Cmx and LmrA.

• One of the key methods to unlocking antimicrobial resistance will be to understand the mechanisms as to howmicroorganisms develop resistance.

• Cell–cell communication and the transfer of resistant genes between organisms represent a greater level ofresistance by the bacteria.

• Efflux pumps and biofilm formation from the bacteria provide an added level of their resistant properties