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1. Modes of action and activities of the b-lactam and glycopeptide classes of antibiotic.

1.1 Introduction

Beta-lactams and glycopeptides are antibiotics that inhibit cell wall biosynthesis by inhibiting the transpeptidation of the peptidoglycan.

Glycopeptides are antibiotics used as the last resource to treat severe infections of gram-positive bacteria. This is because it can cause hepatotoxicity, causing rigorous liver damage. Constant monitoring of the patients' blood is needed to control the level of the drug in their system. Vancomycin is one of the glycopeptide antibiotics and it is an exceptionally large molecule made of rings, as can be observed in figure 1 (Cameron, 2021).

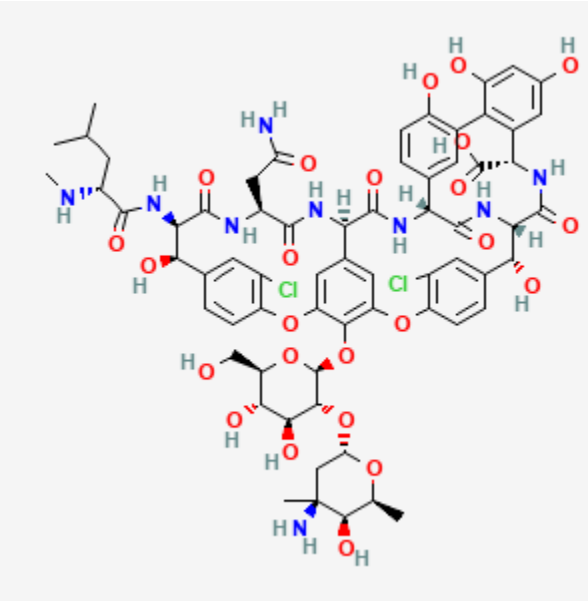

Figure 1. Structure of Vancomycin (ChEBI, 2021).

Beta-lactam is the main antibiotic group that inhibits peptidoglycan synthesis. The characteristic part of their structure is the beta-lactam ring. It is in the center of the structure, and it is made of three carbons and one nitrogen. They are four main different subclasses of this type of antibiotic: penicillins, cephalosporins, carbapenems, and monobactams (Cameron, 2021).

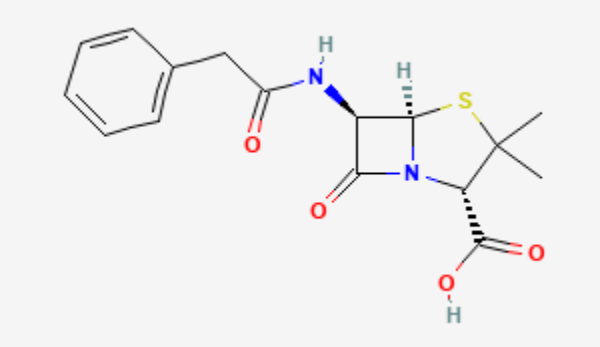

Figure 2: structure of Penicillin (ChEBI, 2021).

1.2 Mechanisms and effects

Both groups of antibiotics have the same mechanism of inhibition, which is the disruption of peptidoglycan synthesis. It involves stopping the process of transpeptidation, peptide bonds forming between adjacent molecules. Antibiotics inhibit the peptide cross-links from forming, leaving the cell wall structure weak and allowing water to enter the cell. Consequently, the cell bursts due to osmosis (Cameron, 2021).

There are several options where bonding can happen in transpeptidation. Gram positives have a pentaglycine linker and most gram negatives have an interpeptide linker between one peptide and the next (Kim et al., 2015; Cameron, 2021).

Vancomycin acts in the transport of nucleotide precursors across the membrane and helps stop the transportation between the cytoplasmic membrane and the periplasm. The glycopeptides bind to D-ala-D-ala at the end of the pentapeptide, therefore transpeptidation is stopped, and cross-linking is prevented (Kim et al., 2008).

The beta-lactams act as a structural analog for D-ala-D-ala. Their structure is similar, but it differs in one compound. This is an enzyme-catalyzed reaction, and it implicates enzymes called DD-transpeptidases to produce peptide links between the molecules and the amino acids. They are also called penicillin binding proteins (PBPs) (Cameron, 2021).

The atoms of the antibiotic structure are in the proper positions to bind to the same place as the DD transpeptidase as D-ala-D-ala. This inhibits cross-linking as the bonds cannot be formed anymore. The antibiotic becomes permanently bound to the enzyme, blocking its activity irreversibly so it cannot catalyze the transpeptidation (Kim et al., 2008).

1.3 Types of bacterial infections

Glycopeptides react against gram-positive infections; their molecule structures are large so they cannot cross the outer membrane of gram-negative infections (Cameron, 2021).

Beta-lactam antibiotics are used to treat different infections depending on the type of antibiotic. Penicillins are active against most gram-positive bacteria. On the contrary, cephalosporins have a higher impact against gram-negatives than penicillins. Monobactams only work against gram-negatives (Percival et al., 2014). Lastly, carbapenems are often used as a last resort for some infections because they are active against a broad spectrum of gram-negatives and gram-positive (Papp-Wallace et al., 2011).

1.4 Antimicrobial resistance

Antimicrobial resistance occurs when microbes mutate, and they are no longer affected by antibiotics or other medicines. The bacteria with antibiotic resistance (AR) compete with other types of bacteria in the site of infection. Usually, the AR bacteria have the same chance of survival in a normal bacterial environment. If the antibiotic is present, the bacteria population is reduced to bacteria with a resistant phenotype, and they will end up colonizing and dominating the infection. The antibiotic used will no longer cause any effect on the bacteria with acquired mutations (Cameron, 2021).

The antibiotic resistance mechanism most successful and in consequence, the most common is the one that the bacteria develop against beta-lactams. This is the enzymatic conversion of antibiotics into a non-toxic form (Cameron, 2021).

Bacteria produce an enzyme called beta-lactamase. The function of this enzyme is to inactivate antibiotics. It attacks the bond between the nitrogen and carbon in the beta-lactam ring, and therefore, the beta-lactam cannot act as a D-ala-D-ala structural analogue. There are different types of enzymes that provide antibiotic resistance such as penicillinase and cephalosporinase (Cameron, 2021).

The other antibiotic resistance mechanism is the modification of a drug sensitive site. It affects both glycopeptides and beta-lactams, more specifically, the penicillin binding proteins. The target protein mutates genetically which leads to a mutation of the protein sequence. Consequently, the antibiotic is still functional, but it is altered sufficiently so the antibiotics cannot bind anymore. If the drug loses its ability to bind and to act as a structural analogue, it is no longer effective. In this way, the binding site of the antibiotic to the cell target is eliminated or reduced (Cameron, 2021).

1.5 Conclusion

Beta-lactams and glycopeptides are antibiotics that target the cell wall. They inhibit peptidoglycan synthesis and prevent cross-linking to protect the human body from bacteria. Consequently, antibiotic resistance can happen due to the modification of the drug site or enzymatic modification.

2. Smallpox and covid-19 vaccination

2.1 Introduction

A disease can be caused by a broad number of microorganisms. A virus is a very small infectious agent with a protein shell surrounding nucleic acids. It is not independently alive as they need a live organism to be able to reproduce, however, viruses are intracellular parasites that are inert outside the host cells. Consequently, cells are damaged, and eventually, it can cause the death of the live organism (Horrocks, 2021).

Throughout history, infectious diseases have spread across the world killing many millions of people. Smallpox was the second deadliest pandemic in history, followed by the black death. One out of three people died from this virus. The infectious disease was caused by the variola virus, and it killed 90% of native Americans and 400000 Europeans annually in the 1800s (LePan, 2021). It was present in nature for at least 3000 years and lasted until 1979 when it was declared officially irradicated (WHO, 2016). Due to the substantial number of people affected, the world health organization (WHO) conducted an intensive global vaccination campaign when the first vaccine ever made was created to end this disease.

Covid-19 has had an enormous impact across the world since its first detection in late 2019 and it was declared a pandemic in March 2020. The disease is caused by the SARS-CoV-2 virus, and it is part of a group of RNA viruses called coronavirus (Astuti & Ysrafil, 2020).

2.2 Disease biology

Smallpox only affects humans, and it is one of the biggest viruses with a measurement of 300-350 nm long. It has a linear double-stranded DNA molecule. The virus has an outer envelope made of proteins and lipids and a core envelope with a dumbbell shape. Surface tubules made of proteins are present on the outer layer (Traktman, 1996). Specific receptors on the host cell membrane are used by the virus to bind and invade the cell. The variola virus uses the host's enzymes to replicate in the cytoplasm. It does not need any help from the host cell to replicate, as the virus codes for all enzymes used for proliferation, making the process much easier and deadly. Once replication is done, it leads to the elimination of the original DNA and other cell changes so the virus acquires control of cell reproduction (Berwald, 2004). Fever and skin lesions were the most prevalent symptoms of the variola virus.

Figure 3: A picture of the variola virus (Kon, no date)

The viral genome has a low mutation rate, and consequently, the variola virus has no antigenic variation (Moss, 2010). Due to the limited ability of the viral DNA polymerase to adapt to humans and its high replicative fidelity, this virus was antigenically consistent and no evolved mutation appeared (Bray & Buller, 2004).

Covid-19 is found in humans and animals. It has a circular shape, and the genetic material consists of a single strand of RNA. The virus SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2, possesses a series of protein spikes on its surface. There are four structural proteins similar to other coronaviruses. Firstly, the envelope proteins play a critical role in viral replication. Secondly, the spike proteins are responsible for the attachment process of the host cell by receptors with high affinity. Thirdly, the membrane proteins define the shape of the viral envelope. Lastly, nucleocapsid proteins are bound to the genetic material, inhibiting the host cell's defense mechanism, and helping in viral RNA replication (AnatomyZone, 2020).

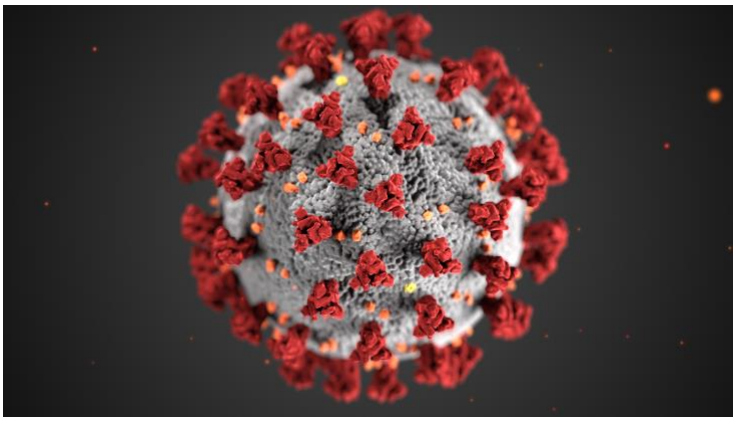

Figure 4: A picture of the virus SARS-CoV-2 (Centers for disease control and prevention, 2021).

Usually, the primary viral replication is located in the mucosal epithelium of the upper respiratory tract, and it then moves to the lung epithelial cells. Unlike the variola virus, SARS-CoV-2 can evolve quickly in

response to the immune system defense mechanisms, creating a significant viral diversity (Rice et al., 2021).

When a virus infects a host, it develops antibodies for that specific viral antigen. Over time, it slowly starts to change, and even if the transformations are only slightly different, they accumulate. When the host is infected again, it does not have the correct antibodies and memory B cells to recognize the viral proteins. This is called antigenic drift (Horrocks, 2021). Due to the process, mutations in the SARS-CoV-2 RNA strains increase antigenic diversity and the immunological memory cannot cope with this new pathogen. This entails a big challenge to get rid of the virus with a single vaccine, as it is not ready to fight against the new mutation of the virus.

2.3 Vaccine development

The first vaccine ever created was to fight against the disease smallpox in 1720. The vaccine used a live virus, but it was made from a poxvirus called vaccinia. This virus proceeds from the same family as the variola virus, but it is less harmful (Centers for disease control and prevention, 2017). In the 1800s the cowpox virus was used for immunisations as well around the United States and European countries. It is shown that only one dose of the vaccine was enough to provide antiviral immunity in a long-lived period (Sadanand, 2020). This attenuated type of vaccine can increase memory cell development and prolong immune epitope exposure. Moreover, only a single immunisation is required. However, the live vaccines can cause a higher risk of adverse reactions and the virus can be reversed to its virulent form (Horrocks, 2021).

There are five different approaches to the covid-19 vaccine. Firstly, the RNA vaccine uses a messenger RNA encoding SARS-CoV-2 surface protein gene and it is translated to produce the protein, so antibodies are produced as an immune response. This type of vaccine is non-infectious, and it has no potential infection risk. Secondly, the DNA vaccine consists of a plasmid synthesised with genes of SARS-CoV-2 surface protein which enters the nucleus of the host cell, and the DNA is transcribed into mRNA to cause the immune response. Thirdly, the viral vector vaccine has different live viruses engineered to carry the surface protein gene. It transcribes the gene in the cytoplasm or enters the nucleus for transcription, and consequently, DNA is transcribed into mRNA to induce the immune response. Fourthly, a live-attenuated vaccine, similar to the smallpox vaccine is also being developed, causing the natural immune response. Lastly, the protein-based vaccine directly triggers the immune response because the SARS-CoV-2 surface protein has already been synthesised and combined with adjuvant to enhance the production of antibodies (Pollard, Bijker, 2021; Connelly, Robinson, 2020).

2.4 Conclusion

Some pathogens can change their genetic material by mutations, however other pathogens do not have that capacity. Smallpox presents no antigenic drift, and for this reason, a single dose of vaccination has been used to eradicate this disease. On the contrary, covid-19 can evolve quickly, and new variants cause new infections in the host cell. Therefore, the eradication of this disease is much more challenging by relying only on vaccines.