HOW DOES ANTIBIOTIC RESISTANCE WORK? THE MECHANISMS OF ANTIBIOTIC RESISTANCE

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ABSTRACT
Antibiotic resistance occurs when bacteria survive in the presence of antibiotics, which are generally used to kill bacteria. This resistance has become a growing issue in several industries, including healthcare, where bacterial infections have become more difficult to treat. With antibiotic resistance rising to be a threat to the health of humans and animals, it is essential to understand how antibiotics work and how bacteria are able to bypass their effects. Antibiotics primarily serve their purpose by breaking apart the bacteria or interrupting necessary processes for survival. Bacteria, once they acquire resistance through either mutation or uptake of foreign DNA, use many strategies to counteract antibiotics. Currently, there are various approaches being researched to prevent or work around antibiotic resistance. With the increasing prevalence of resistance, this research is crucial to reverse its impact.

INTRODUCTION

Antibiotics are drugs that are used to kill bacteria and to prevent bacterial growth. In healthcare, antibiotics are commonly utilized to treat bacterial infections. However, improper use of these drugs can lead to a phenomenon known as antibiotic resistance, where some bacteria are able to withstand the effects of antibiotics, furthering growth and proliferation. Such a situation can be deadly to any infected human or animal (U.S. National Library of Medicine, n.d.). Because of its detrimental impact, it is important to understand how antibiotic resistance arises, how it works, and how it can be prevented or bypassed to ensure infections are no longer resistant.

HOW ANTIBIOTICS KILL BACTERIA

Antibiotics were first discovered as naturally occurring compounds in certain organisms. Penicillin, the first discovered natural antibiotic, was isolated from a mold species (Gaynes, 2017). Today, most antibiotics are chemically modified versions of natural antibiotics (Pancu et al., 2021). Just as bacteria vary in structure, most antibacterial activity is categorized into one of five different mechanisms. Despite being distinct processes, each has a similar effect: killing the bacteria or terminating their growth.

Antibiotics can interrupt bacterial cell wall synthesis. The cell wall in bacterial cells provides structure. An antibiotic can cause this wall to break to prevent cell wall synthesis. As a result, the cell can no longer control its structure. In such a situation, the bacterium is unable to sustain itself (Uddin et al., 2021).

Antibiotics can also inhibit bacterial cell membrane function without breaking down the cell wall. The membrane of a cell is a thin layer within the cell wall primarily composed of lipids with some carbohydrates and proteins attached. The membrane selectively allows certain molecules to enter or exit the cell, which help the cell to perform processes that keep it alive and help it grow. If the cell membrane is not functioning properly, the bacterium cannot control the environment within its cell. The change in environment interferes with the bacterium's own workings, causing the cell to die. Some antibiotics specifically target glycolipids—lipids with an attached carbohydrate—to destroy the membrane (Uddin et al., 2021).

Some antibiotics can disrupt the mechanisms of protein or nucleic acid synthesis, both of which impact the bacteria's well-being in a similar manner. Nucleic acids, such as DNA, are processed to synthesize proteins. Without proper synthesis of nucleic acids, it is impossible to make proteins, which are essential for various functions within the cell. Lacking necessary proteins, the bacteria can no longer stay alive. Additionally, both nucleic acids and proteins are important for the growth and replication of bacteria. If neither of these molecules are synthesized, bacteria cannot proliferate.

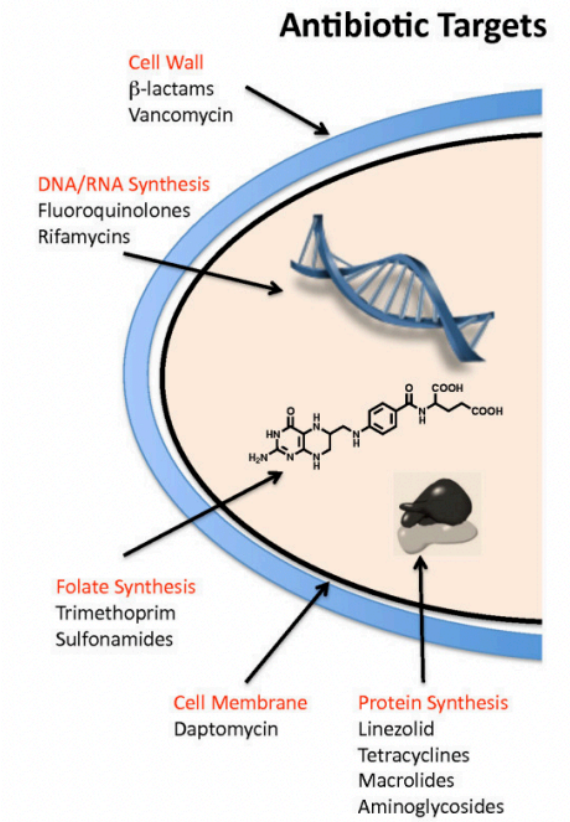

Figure 1: Antibiotic targets in bacteria (Wright, 2010)

Other antibiotics can inhibit metabolic pathways in bacteria through degradation or modification of molecules involved in these processes. Metabolic pathways are ever-present in not only bacterial cells, but in every cell, consisting of all the chemical reactions that keep cells alive, including the conversion of food to energy. By disrupting these processes,

antibiotics effectively block bacteria from sustaining themselves (Uddin et al., 2021). However, in the face of antibiotic resistance, any antibiotic efforts can be deemed useless.

HOW ANTIBIOTIC RESISTANCE IS ACQUIRED

There are various mechanisms used by bacteria to protect themselves against antibiotics, but how is this resistance acquired? Bacteria generally use one of two major genetic strategies to attain this resistance against antibiotics: mutations or acquisition of foreign DNA (Munita and Arias, 2016).

Random mutations in DNA can have substantial impacts. Certain bacteria may acquire a mutation that changes how they interact with the antibiotic, which may cause the antibiotic to be less effective. As some bacterial cells attain this mutation, they survive against the antibiotics and proliferate. The cells without the mutation are still killed. Consequently, this gives the resistant bacteria more resources, such as habitat, space, and nutrients, to grow at an even faster rate. Eventually, most of the cells will be mutated to be resistant to the antibiotic (Munita and Arias, 2016).

Another way bacteria can attain this resistance is through horizontal gene transfer. Horizontal gene transfer is the movement of genetic information between two distinct bacteria. This could mean that two bacteria physically connect, allowing DNA to move from one organism to another. A bacterium can also uptake DNA floating in its environment. In nature, this DNA comes from dead bacteria, which release their contents outside of the cell (Kloos et al., 1994). Any of these methods would lead to the exchange of genetic material amongst bacteria that are not related through a parent-offspring connection. This allows bacteria with resistance to pass on their ability to other cells. This way, an increasing amount of cells can acquire the resistance.

THE DIFFERENT MECHANISMS OF ANTIBIOTIC RESISTANCE

There are four broad categories of processes through which bacteria act upon their resistance to antibiotics: modifying the antibiotic molecule, preventing the antibiotic from reaching its target, changing target sites, and undergoing global cell adaptations. Each of these categories can be further broken down into specific mechanisms.

Bacteria, once resistant, can modify the antibiotic through chemical change to prevent it from harming the cell. In this process, the bacterial cell acquires a gene that produces certain enzymes, which are proteins with catalytic functions. Enzymes are able to speed up or push certain chemical reactions. In this case, the enzymes can change the antibiotic molecule so that it no longer functions. Some bacteria produce enzymes that completely destroy the antibiotic molecule. As of now, it is thought that there are over 1,000 different enzymes capable of this function (Munita and Arias, 2016).

Bacteria are also able to prevent the antibiotic from penetrating the cell wall or efflux the antibiotic out of the cell. Many antibiotics target areas in the cell membrane, meaning these antibiotics need to penetrate the membrane in order to perform their function. Several bacteria develop efficient membranes that act as barriers against antibiotic uptake. Other bacteria develop complex machines in the bacteria cell membrane that work to extrude toxic compounds out of the cell, known as efflux pumps, which work against antibiotics. These pumps can have strict or broad substrate specificity, which refers to the range of molecules the pump is able to recognize (Munita and Arias, 2016). In these ways, the cell is able to protect the cell membrane from antibiotics, which, in turn, keeps the bacterium alive.

In the case of target-specific antibiotics, which act at a specific target site on the bacterial cell, the bacterium is able to interfere with the site to achieve resistance. One method is to protect the target. Through this, the bacteria contain molecules that bind to the target site, preventing the antibiotic from reaching it. Bacteria can also modify the target site, preventing the antibiotic from recognizing the site. Target site modification can be achieved by inducing mutations in the genes that encode the site. It can also be achieved by using enzymes to chemically alter it, or by replacing the original target with a different one (Munita and Arias, 2016). Any of these methods work to deter the antibiotic from interacting with its

target site, allowing bacteria to resist the effects of the antibiotic.

Lastly, bacteria can go through global cell adaptations that lead to antibiotic resistance. Through generations of evolution, bacteria can develop ways to deal with environmental pressures to survive against detrimental environments. For example, bacterial organisms inside of a host are constantly attacked by the host's immune system. Over time, these bacteria are able to adapt to the stress in their environment and develop complex mechanisms to prevent the disruption of important cell processes, such as cell wall synthesis and membrane homeostasis (Munita and Arias, 2016). After many years of adaptation and evolution, bacteria can survive hostile conditions, including those created by antibiotics.

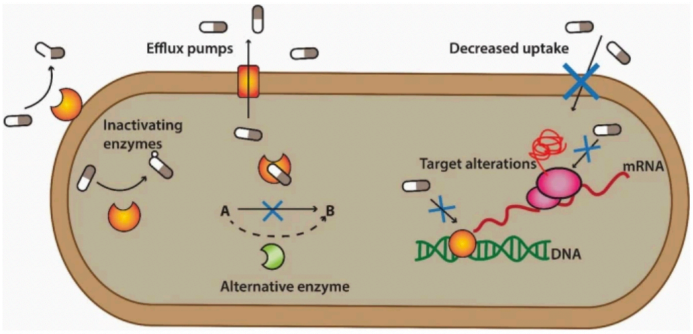

Figure 2: Mechanisms of antibiotic resistance in bacteria (Mutuku et al., 2022)

STRATEGIES TO COMBAT ANTIBIOTIC RESISTANCE AND THE FUTURE

It is important to understand how antibiotic resistance works in order to combat its harmful effects. Although many of the mechanisms of antibiotic resistance are known, there are many that are yet to be discovered. Despite this, researchers are working to find ways to prevent and reverse antibiotic resistance, which has been emerging quickly.

One researched method to counter antibiotic resistance is to use the CRISPR-Cas9 system. CRISPR-Cas9 can be used to detect and modify genes that confer antibiotic resistance to deactivate. Currently, research has shown that CRISPR-Cas9 can change the structure of bacteria. In a study by Citorik and collaborators, a mouse model was used to determine how well Cas9 can be used against bacteria (Uddin et al., 2021). Cas9 is a protein that functions as molecular scissors to modify genes. Through this study, it was determined that CRISPR-Cas9 can work in certain situations. Unfortunately, as the complexity of bacterial communities increases, it becomes difficult to use these methods accurately and successfully.

An important part of the research to combat antibiotic resistance has been the use of bioinformatics, which includes all the different models that are used to identify and understand molecules. Many methods in the field of bioinformatics can be insightful about bacteria and antibiotic resistance, some of which are currently being used to develop drugs against bacteria with antibiotic resistance. One of these methods is whole genome sequencing (WGS): the use of various methods to analyze the entire genome, or DNA, of the bacteria. This provides information about how the DNA codes for various proteins that lead to resistance (Uddin et al., 2021). WGS allows us to understand the bacterial genome so that drugs can effectively target the correct proteins related to antibiotic resistance. Another method within bioinformatics is using machine learning tools to predict antibiotic resistance. WGS can be used along with prior knowledge to utilize already understood pathways towards resistance to predict new pathways and mechanisms.

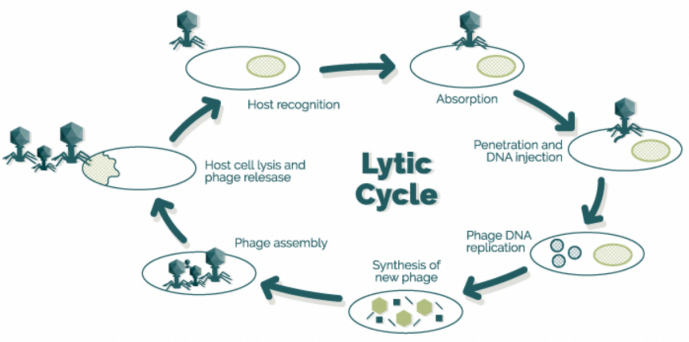

Figure 3: Bacteriophage infection and lysis of bacteria (Coliphages, 2024)

Another found method to combat antibiotic resistance involves the use of bacteriophages, which are viruses that infect bacteria. Phages are used to insert antibiotics directly into target

bacteria without affecting surrounding cells. Many phages are lytic, meaning they enter the bacteria, use the bacteria's resources to replicate, and then exit the bacteria, leaving it to die (Uddin et al., 2021). Moreover, in another study, it was found that the use of bacteriophages along with antibiotics led to more successful control of bacterial growth than either method alone (Łusiak-Szelachowska et al., 2022). These methods, if specified to be unharmful to cells that are not bacteria, may be a powerful alternative or additive to antibiotics.

CONCLUSION

As antibiotic resistance becomes more prominent in bacteria, it is critical to find alternative methods. Antibiotics are a common measure to kill bacteria in various fields. Unfortunately, increased usage of antibiotics has led to difficulties in battling antibiotic resistance, which leads to continuing problems in healthcare as diseases and infections are left without effective treatment.

Antibiotic resistance may be a random occurrence, but it is one that adapts quickly through populations of bacteria. Through antibiotic resistance, bacteria are able to survive, replicate, and infect. This prevalent resistance makes it crucial to understand how bacteria acquire this resistance and how it can be prevented or bypassed through other methods.

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