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The Role Of The Immune System Against Antibiotic Resistant Bacteria

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Abstract

Antibiotic resistant bacteria has slowly made a larger appearance in many corners of the world and has influenced global health. This is because of misuse or overuse of antibiotics in humans and agriculture. Many have died to seemingly harmless and easily curable diseases due to the resistance, and there has been a call to reduce the usage of antibiotics altogether. We are now forced to find alternatives, and some researchers have looked into the immune system, and specifically, how to optimise its current response against bacteria. The immune system generally responds with the complement system, phagocytosis and inflammation. By using other medications that boost the immune response, we may be able to curve away from antibiotic resistance prevalence in bacteria worldwide.

Keywords: Antibiotic resistance, Complement system, Phagocytosis, Inflammation, Autophagy

Introduction

The human immune system is one of the most complex biological systems we know of.[1] Spread throughout the entire body, its own network reaches every organ, tissue and cell, with roughly 70% of all the immune cells concentrated in the gut.[2] One key organ in the immune system is the bone marrow, where production of most immune cells in the body occur; The bone marrow alone produces an estimated 500 billion mature blood cells daily.[3,4]

One microorganism that the immune system protects the human body from is bacteria. Bacteria, the smallest known life form, are unicellular organisms that cover the earth. Many are harmless to humans, sometimes even helpful, however there are a number of exceptions that cause diseases, such as Cholera, Lyme borreliosis, and Tetanus.[5-8] These bacterial infections are usually treated with antibiotics, due to their extreme effectiveness. Antibiotics, regarded as one of the most influential medical breakthroughs of all time, made difficult diseases into something curable, and became a common sight in hospitals and pharmacies worldwide.[9-11]

This increase in using antibiotics may have caused the prevalence of many bacterial infections to decrease, but a drawback was soon identified. Antibiotic resistance or when a microorganism such as bacteria or fungi develops immunity against the drugs that were created to kill them developed into a huge problem.[12] Easily-treatable infections warped into incurable and fatal diseases. In 2019 alone, an estimated 1.27 million deaths were directly related to antibiotic resistant bacteria.[13]

There are many causes of antibiotic resistance, but the two main contributors are over usage of antibiotics in human health and in animal production. The factors of those two causes are related to a lack of educational programmes on hygiene, health and a lack of appropriate doses of antibiotics.[14] This global crisis has impacted health all over the world, where illnesses became more severe, ranking up costs and letting patients suffer from adverse side effects from more powerful medications.[15]

One method to combat antibiotic resistance is to create and moderate guidelines in antibiotic usage. This is to reduce and educate people on antibiotics and antibiotic resistance.[16] However, with this, we must find other novel methods to combat bacteria, and especially, antibiotic resistant bacteria. However, there are a number of questions unanswered that would help researchers in this development. One question is how antibiotic resistance is formed in the first place inside the human body, and how our immune system reacts to it.[17] If we are able to map out the pathway of how the immune system responds to an antibiotic resistant bacteria, it will be extremely beneficial to the development of a newer and effective treatment.

The immune response against a normal bacteria infection

Bacteria must first enter the human body for an infection to occur. This can happen if the host and the bacteria share an environment together. Bacteria can enter through air, water or food.[18] Once in the body, bacteria releases chemicals named toxins that damage cells.[19] These toxins interfere with a cell and manipulate them to help the infection; They can obstruct the the host cell membrane, inhibit protein synthesis, and much more.[20,21]

This invasion is then detected by our innate immune system, either by recognizing host signal molecules that are released after being damaged by human cells or pathogen-associated molecular patterns [PAMPs].[22] Our innate immunity is taken from our mothers, and includes natural barriers as well as immune cells. The primary function of the innate immune system is to respond quickly and effectively, eliminating the threat as well as maintaining homeostasis in the human body. [23,24]

There are many methods in exterminating bacteria, to which some work together as a team, while other processes are singular and can happen on their own.

The complement system

Complement proteins are one of the first responders or immune proteins when a bacteria is detected. There are three pathways on how they enter the scene. First, the classical complement pathway.[25] Antibodies are sent and bind with the antigens on the bacteria's plasma member. These antibodies are then targeted by the immune complement proteins and they bind together to create a complex or the membrane attack complex [MAC]. MAC is similar to a doorway, allowing for substances to enter and exit the bacterium. The opening or pore they opened allows the entry of lysosomes, weakening the bacteria to at risk of lysis.[26]

Another option is the lectin pathway. Comparing it with the classical pathway, it's very similar in tems how it's activated. Unlike the classical complement pathway, instead of binding with antibodies, mannan-binding lectin [MBL] binds to proteins or hexoses such as glucose, fructose and especially mannose.[27] These structures of sugars are often repeated on bacterium's surfaces, which displays why MBL binds to it in the first place. [28]

The last pathway is the alternative complement pathway. Unlike the classical one, it does not need any help from antibodies to make bacteria susceptible to lysis. Instead, the complement proteins form a complex directly on the bacterium's surface. This ends up with the formation of MAC yet again. It provides an alternate but direct pathway, unlike the other two, and is known to amplify the final effectiveness of the immune response. [29]

Phagocytosis

Phagocytosis is the process of digestion of foreign cellular components as a form of elimination of the threat and the protection for the body. This process is carried out by a handful of cells, but there are certain immune cells who are specialised in doing this. To name a few, there are macrophages and neutrophils.[30]

Macrophages are phagocytes that mainly handle the clean up of dead or diseased cells, rather than invaders. They ingest microbes, material and tumour cells and help control internal conditions as homeostasis as regulators. However, they do play a part in immunity. Macrophages are found in all tissues of a vertebrae, and help host protection by being effector cells. They are competent in being able to identify foreign antigens and alert T cells for cell mediated immunity. Due to the rapid speed of the innate immune system, occasionally, the macrophages kill the bacteria themselves before notifying T cells for assistance in the form of antibodies. [31]

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Unlike macrophages, neutrophils' main functionality is to kill foreign pathogens. They are deemed the most efficient phagocyte, being able to engulf and destroy moreover 50 bacteria at a time. [32] They eradicate both bacterial and fungal pathogens via phagocytosis. They recognize microbial pathogens with their surface pathogen recognition receptors [PRRs], such as toll-like receptors [TLRs] or opsonic receptors. Their pattern recognition allows the host body to store information about what has occurred and what pathogens or antigens they have seen before. With that, neutrophils are important in creating a link or connection between the innate immune system and the adaptive immune system. This relationship or linkage is vital for long-term protection, in case the host interacts with the same strain of bacteria once again. [33]

The inflammatory response

The inflammatory response is similar to a bomb detonation since it leads to the destruction to both microbes and the host cells. Inflammation's primary role is to subside an infection or restore damaged tissues to return to balanced homeostasis. [34] In the case when bacteria attacks and harms the host's tissues, the tissues release chemicals. These chemicals affect the blood vessels, where it redirects them into the tissue to fill in the leftover space. This causes inflammation. This swelling of tissue helps create a barrier which separates forgein substance from the rest of the body. These chemicals also send signals to immune cells or phagocytes to get rid of the intruder. [35]

The chemicals involved in the inflammatory response are called the cytokines, and are the key modulators in this response. Examples of cytokines are chemokines and interferons.[36] Chemokines are responsible for chemotactic activities, or the movement of certain substances or microorganisms resulting from the effect of a chemical stimuli. In certain cases, they instruct cells, both immune and non-immune, on what to do.[37] Interferons do not have a clear primary function, and have a diverse course of action depending on the strain of bacteria it is up against.[38]

Despite its high effectiveness, there is a large setback in inflammation, the cytokine storm. Cytokine storms occur when the immune system hyperactivates immune cells to release a considerable number of cytokines, leading to a raised level; with positive feedback, more immune cells are called or triggered, thus amplifying the entire response. This amplification is problematic to the entire body, leading to clinical conditions or organ damage.[39,40]

The causes of Drug Resistant Bacteria [DRB] / Antimicrobial Resistance [AMR]

Drug resistant or antibiotic resistant bacteria is natural, and arises as an adaptation of the bacteria in response to these medicines. Due to humans' increase in the usage of these medicinal drugs, this natural process was accelerated where it exceeded the production rate of newly discovered drugs. This situation formed a global crisis where infections are now harder to treat because people are now dealing with superbugs that are practically immune to all commercial drugs.[41-43]

All microorganisms have one goal; survive. They want to be able to pass on their genes by means of reproduction and spread. They adapt in order to maximise their chances of survival according to the environment. There are other modern causes of the elevated prevalence of antimicrobial resistance [AMR], which contribute by altering major aspects of the bacteria's surroundings.[44]

Misuse or overuse of antibiotics in humans

Ever since the discovery of antibiotics, it has been used to treat infections worldwide. It isn't just used as a singular treatment, but also a component in other medicinal transactions such as chemotherapy or surgery. It's a staple in the medical community.[45] Due to its mass availability and easy access, antibiotics have been used or prescribed inappropriately.Roughly 50% of all medicines worldwide are dispensed incorrectly.[46]

Inappropriate use is a broad umbrella term for all mistakes or mishaps that occur when taking an antibiotic. Some examples include unsupervised medication, too much or too little consumption, or over-the-counter [OTC] antibiotics that do not need a prescription to be given out.[47] This overprescription or magnified usage of antibiotics in cases where it's not necessary such as viral infections, is positively correlated with adverse effects, higher hospital readmission rates, and elevated intensity of infections.[48] The misuse of antibiotics sped up the

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adaptation of bacteria's susceptibility to the drugs, making infections harder to treat.

Agricultural use

The global population has exploded in the past century. People were forced to seek out methods to maximise agricultural yield to feed the entire world. Intensive farms were invented for maximum efficiency, completely disregarding all animal and human ethical considerations. This resulted in findings of antibiotic residues in animal products, such as meat [beef, chicken, or pork], or dairy products derived from cows. This in turns increased the accidental intake of antibiotics in areas where it was not necessary, thus contributing to the antibiotic resistance crisis.[49]

Antibiotic resistance can transverse through different ecosystems and different species. Soil, plants, farm animals and humans are all connected in a food chain, which gives the antibiotic resistant genes and bacteria means to pass through without limitations. Antibiotics are used in farm animals to improve growth and cure diseases quickly. Complete absorption does not occur in their bodies however, and antibiotic residues are passed down into their faeces or urine. Most of these waste products are recycled away as fertilisers or manure, which is used in crop production. These crops are then fed to the livestock and the cycle repeats.[50]

Lack of new antibiotics

In recent years, there has been something known as the "innovation crisis" floating around in the pharmaceutical industry. A survey conducted in 2021, explained that the causes of the innovation crisis is the rise in research costs and reduction of productivity of researchers. It's also related to the current difficulty of science, different motives in research teams, and the scattered areas of knowledge that are needed to be intertwined for research.[51]

The investment of antibiotic treatments has diminished by both public and private sectors. The issue is that, the more superbugs we create with the current treatment, the less options the patient has to use as treatment. "We are running out of options," explains Hanan Balkhy, WHO Assistant Director-General for Antimicrobial Resistance.[52] Without ways to kill these antibiotic resistance bacteria, the more they replicate and spread, passing on their resistant genes to next generations and heightening the presence of them.

How the immune system helps tackle drug-resistant bacteria

Drug resistant bacteria may have the upper hand against our usual treatment, but they are not susceptible to the immune system. They need to do a trade-off, where they either develop immunity against antibiotics or our immune system. There is no cross-resistance to antibiotics to our immune mechanisms, alongside our other key players such as the bacteriophages.[53]

With that information, many researchers have investigated using a new method of treating antibiotic resistant bacterial infections named host-directed therapy [HDT]. Unlike our current treatment where we solely depend on drug dosages, HDT aims to strengthen the immune system's response to kill bacteria. However, as we stated in chapter 2.3, the inflammatory response is incredibly powerful on its own. Amplification of inflammation can overproduce immune proteins is a source of multi-organ failure and the death of the host human.[54] HDT has been utilised to aid antibiotic resistant tuberculosis [TB] . The particular problem with tuberculosis is its time-consuming treatment. For patients who suffer from multi-drug resistant [MDR] tuberculosis, it can take up to two years for the infection to fully subside.[55]

Another method that enhances the immune system rather than targeting the bacteria itself is antibody combination therapy. Antibody combination therapy is the treatment that uses different antibodies made by the immune system for identification, elimination or infringing on the development of certain cells such as tumour, infected or cancer cells.[56] It has been linked to reinforce the complement system's pathways in defeating bacteria.

Autophagy, Phagocytosis, and Inflammation in Host-Directed Therapy

Autophagy is the body's self-cleaning mechanism similar to the phagocyte's phagocytosis. The difference is that phagocytosis is the process of engulfing waste materials or foreign substances to destroy them, but autophagy is the process of removing waste materials from the inside of the cell for degradation. Autophagy's targets are either degraded into lysosomes, or released by exocytosis.

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Essentially, Autophagy is the process supplying phagocytes with the substances it destroys.[57] When bacteria attempts to enter the host's cell, xenophagy happens. Xenophagy is when the intruder, in this case the bacteria, is "identified as targets of selective autophagy".[58] The bacterium is then covered with a vacuole or membrane to restrict their growth or replication processes. After this, they are subjected to either a lysosome, creating an autolysosome, or pushed out via exocytosis.[59]

Autophagy is also involved with inflammation by determining the survival of inflammatory cells as well regulating the level of cytokines secreted. Autophagy affects macrophages by promoting the production of cytokines and chemokines, but also helps bacterium termination via creating an autolysosome. It also modulates the macrophages' survival, by programming their cell death when they have ingested too much. In the scenario where a cytokine storm happens, autophagy tends to be the process that helps reduce the general impact of it.[60]

In HDT, researchers have looked into the regulatory abilities of autophagy targeting therapeutics against bacterial infection. Currently, the therapeutics that can regulate these pathways are TFEB, FOXO and NRF, and are good contenders since they specifically target phagocytes. These drugs in HDT have been tested and confirmed to induce autophagy in infected host cells which helps with clearance of tuberculosis, reducing the time it stays in the body and the risk of re-infection.[61,62] Since these drugs are not antibiotics, they will not contribute to the antibiotic resistance crisis and will be effective towards drug resistant bacteria in general.

The Complement System in Antibody Combination Therapies

Due to the number of antibodies, it can create an imbalance in the complement system. As mentioned in 2.1, the classical complement pathway depends on antibodies and their linkage to antigens on the bacterium's plasma membrane. Antibodies either inhibit or stimulate the complement system. In some scenarios, inhibition of the complement system leads to good outcomes, such as in sepsis, degenerative diseases or autoimmune diseases. To focus on bacteria however, the stimulation aspect of antibodies is much more influential.[63]

A portion of bacterial pathogens inhibit complement by altering their membranes to trick the complement cascade by being similar to other cells that aren't targets of the immune system. Antibodies are specific, and if we deploy pathogen-specific antibodies, it could entail the inhibition of the pathogen's membrane. With specific antibodies, we are able to successfully eliminate the bacteria by stimulating the classical complement pathway into recognizing and killing the undetected bacteria.[64]

To increase the effectiveness of this therapy, we must target multiple proteins via antibody "cocktails" or bispecific antibodies. Granted, this treatment is relatively new, and these technologies are being tested, but it is a promising strategy and can possibly be a staple in the medical community. Currently, there are two existing antibody combination therapies approved for clinical use in hospitals, trastuzumab and pertuzumab.[64]

Conclusion

Antibiotics may have been the golden and standard method in treating bacteria, however the increased frequency of antibiotic resistant bacteria, this treatment went bleak. Due to the lack of new antibiotics, we are in urgent need of a new approach for treating bacteria. By mapping out how the immune system goes against bacteria on its own, we may be able to develop a treatment that uses the strong aspects of the immune system, rather than killing the bacteria for the immune system.

The big three strands of the immune system regarding preventing bacterial infection are the complement system, phagocytosis and the inflammatory response. All of these features are improved via other medicinal drugs and therapies such as host-directed therapies and antibody combination therapies. We have seen these treatments used against tuberculosis, and are on a clear track to success with some antibodies already being approved for human use. If we were to stray from antibiotics, we should support our immune system due to its promising results that it has yielded in defeating drug-resistant bacterias. This will help us slow down or avert the crisis of antibiotic resistance altogether.

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