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Mycobacterium Tuberculosis Resitance Mechanisms to Bactericidal Activity of Phagocytes: A Review

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Abstract

The human immune is extremely complex. It has evolved over hundreds of millions of years to respond to invasion by the pathogenic microbes that regularly attempt to infect our bodies, and invasion by the microbes that tried to infect our genetic ancestors. Phagocytes are the soldiers of the immune system, and provide innate immunity. They are responsible for swallowing, killing and digesting invading microbes by phagocytosis. Despite the presence of antimicrobial host factors (from immune system), many pathogens such as Mycobacterium tuberculosis can survive inside the host cell due to evolvement of multitude of strategies to counteract host defense mechanisms. The paper review the strategies adopted by Mycobacterium tuberculosis to evade bactericidal activity of innate immune phagocytes.

Keywords: *Bactericidal activity, innate immunity, Mycobacterium tuberculosis, phagocytes*

Introduction

The human immune is extremely complex. It has evolved over hundreds of millions of years to respond to invasion by the pathogenic microbes that regularly attempt to infect our bodies, and invasion by the microbes that tried to infect our genetic ancestors [1]. There are similarities between the immune system of humans and those of the most primitive of vertebrates, going back five hundred million years on the evolutionary ladder [2]. The immune system does not rely on one single mechanism to deter invaders, but instead uses many strategies. The main division between the strategies is that between innate immunity, which does not require previous exposure to the invading microbe, and Acquired immunity, whereby the immune system "remembers" how to deal with a microbe that it has dealt with before [3]. Phagocytes are the soldiers of the immune system, and provide innate immunity. They are responsible for swallowing, killing and digesting invading microbes. The process of swallowing microbes is known as phagocytosis [4].

Despite the presence of antimicrobial host factors (from immune system), many pathogens can survive inside the host cell. Such pathogens, which include bacteria, fungi and viruses, have evolved a multitude of strategies to counteract host defences. Some bacterial species interfere with the ability of phagocytes to engulf them [5,6], either by scavenging, inhibiting or even degrading opsonic antibodies or complement [7,8,9], or by directly impairing the phagocytic machinery of macrophages and neutrophils [5,6,10]. Other bacteria have become resistant to one or more of the antimicrobial factors of phagocytes. Some species have developed metabolic pathways to counteract acid accumulation inside phagosomes or have acquired uniquely resistant proteins to withstand the low pH [11,12]. Yet other bacteria protect themselves by actively degrading [13] or shielding themselves [14,15] from the antimicrobial peptides and proteins produced by phagocytes, or by expressing detoxifying enzymes, such as catalase, that neutralize ROS and/or RnS [16,17]. Alternatively, some bacterial species prevent RnS and ROS formation

by impairing recruitment of the proteins that mediate their synthesis [18,19].

Other species have devised means of overcoming the scarcity of iron by secreting specialized iron-scavenging molecules called siderophores, which sequester and target the cation for bacterial use [20], or by expressing iron storage [21] or transport proteins [22]. Lastly, many bacteria improve their intraphagosomal survival by mounting a vigorous stress response to dispose of and replace damaged proteins [23]. Although most bacteria use one or more of these resistance mechanisms, only a select group of bacteria are 'professional' intracellular pathogens. These species survive and replicate inside phagocytes, effectively avoiding attack by their antimicrobial factors. To accomplish this feat, such pathogens have evolved multiple strategies towards one common goal: to perturb phagosomal maturation [24]. These different strategies are exemplified by the mechanisms used by *Mycobacterium tuberculosis*. Mycobacteria are most usually found as Bacilli, or rod-shaped bacteria. Their cell walls are surrounded by thick waxy coat, which protects them in harsh environments. Sometimes, they shed their cell wall. In this case they are known as the Spheroplast form of the bacteria [25]. Mycobacteria are extremely hardy. They are highly resistant to germicides, because of their thick protective cell wall. They are highly resistant to drying, and can exist outside the body without moisture for long periods [24]. This organism parasitize host cells by arresting or reprogramming phagosomal maturation, by escaping maturing phagosomes or by withstanding the microbicidal properties of the phagolysosome [25].

The Human Immune Systems

Like other vertebrates, humans have two types of immune systems for protection against pathogens. One of the immune systems is called the innate immune system. The innate immune system is also present in most other life forms. In vertebrates, this system employs phagocytes as one of its lines of defense. The innate immune system is called that because the instructions for its operations are written into species' genetic codes. This system is effective from the beginning of an individual's life, and it reacts to pathogens that have been around for millennia. This is in contrast to the adaptive, or acquired, immune system, which is unique to vertebrates, and is their second immune system. It adapts to pathogens that the individual organism is exposed to during life [26].

The adaptive immune system takes longer to respond to threats than the innate immune system, in part because it is much more specific in its response to threats. The adaptive immune system is the one that humans rely on when receiving vaccinations in order to avoid becoming ill in the future with influenza, smallpox or numerous other infectious diseases [27]. The adaptive immune system is also responsible for the confidence a person has that they will never again become infected with chicken pox, for example, because they were sick with it when they were six years old. In this second kind of immune system, there is a first exposure to an infectious agent, called an antigen, either through illness or vaccination. That first exposure teaches the adaptive immune system to recognize the antigen. If the antigen invades another time in the future, receptors on the surface of the antigen will trigger a series of immune responses tailor-made for that specific strain of infection. Phagocytes, however, are primarily involved in the innate immune system [28].

The First Line of Defense

Before the phagocytes become involved in the fight against pathogens as part of the innate immune system, the body uses a less costly line of defense that consists of physical barriers and chemical barriers. The environment is full of toxins and infectious agents in the air, water and food. There are a number of physical barriers in the human body that block or expel invaders. For example, both mucus membranes and hairs in the nostrils prevent debris, pathogens and pollutants from entering the airways [29]. The body flushes toxins and microbes out of the body in urine, through the urethra. The skin is coated with a thick layer of dead cells that block pathogens from entering through pores. This layer sheds frequently, which effectively removes any potential microbes and other pathogens clinging to the dead skin cells [30].

The physical barriers make up one arm of the first line of defense in the innate immune system; the other arm consists of chemical barriers. These chemicals are substances in the body that break down microbes and other pathogens before they can cause harm. Acidity on the skin from oils and sweat prevent bacteria from growing and causing infections. The highly acidic

gastric juice of the stomach kills most bacteria and other toxins that might be ingested – and vomiting acts as a physical barrier to remove pathogenic agents such as "food poisoning," as well. Working together, the ever-vigilant chemical and physical barriers do a great deal to keep out many of the microscopic dangers of the environment that attempt to enter the body and cause harm [28].

The Phagocytes

Phagocytes are the soldiers of the immune system, and provide innate immunity. They are responsible for swallowing, killing and digesting invading microbes. The process of swallowing microbes is known as phagocytosis [31]. There are two main types of phagocyte

Microphages

These cells are also known as Polymorphonuclear Leucocytes, PMNs and Polymorphs. These cells start life in the bone marrow. They are constantly circulating in the blood. They cannot replicate, and live for only a few days. The bone marrow contains large reserves of microphages [32].

Macrophages

These cells start out life as monocytes, which originate in the stem cells in the bone marrow, but when they are first called into action, they turn into macrophages. Macrophages are not as numerous as microphages, and there are no large reserves of them, but they are longer lived than microphages. Macrophages are stationed at strategic locations throughout the body, usually in places that are not otherwise well defended. These areas include the alveoli of the lungs, the abdominal (peritoneal) and chest (pleural) cavities, under the top layer of the skin and the intestines. Macrophages are the front line of defense against microbial invasion in these areas [32].

As mentioned above, the process of swallowing of microbes by the phagocytes is known as phagocytosis. After the invading microbe has been ingested, the next task for the phagocyte is to kill the microbe [31]. This is achieved in two main ways. Aerobically, i.e. using oxygen; the phagocytes produce oxygen based chemicals that are highly disruptive to the swallowed microbe. Oxygen is highly chemically reactive, and these oxygen based chemicals "tear" the microbe apart. This process is known as the oxidative burst, or the respiratory burst and anaerobically, i.e. without using oxygen. One way to kill the microbe without oxygen is by using a chemical that deprives the microbe of iron, thus preventing it from metabolizing. Another way is to increase the acidity of the internal environment of the phagocyte [28].

When these tasks are complete, the Macrophages have one further task to complete. They return to the lymph nodes, displaying the remnants of the destroyed invader on their surface. This has the effect of stimulating the cells of the Acquired immunity system into action [32].

Macrophages Are First Responders

One of the first responders of the innate immune system are macrophages, one of the types of phagocytes. They are very non-specific in their targets, but they respond to any of the 100 to 200 PAMPs known to the innate immune system. When a pathogen with a recognizable PAMP binds to a toll-like receptor on the surface of the macrophage, the macrophage's cell membrane begins to expand in such a way that it engulfs the microbe. The plasma membrane closes so that the microbe, still bound to the toll-like receptor, is held inside a vesicle called a phagosome. Nearby, there is another vesicle inside the macrophage called a lysosome, which is filled with digestive enzymes. The lysosome and the phagosome, which contains the microbe, merge together. The digestive enzymes break down the microbe [33].

The macrophage uses any parts of the microbe it can and disposes of the rest by expelling the waste via the process of exocytosis. It saves pieces of the microbe called antigen fragments, which are bound to molecules specifically designed to display these fragments. They are called antigen-presenting MHC II molecules, and they are inserted into the macrophage's cell membrane, as a crucial step in the adaptive immune system. This serves as an activating signal to the cellular players in the adaptive immune system about precisely which strain of pathogen has invaded the body. As part of the innate immune system, however, the macrophage's primary purpose is to seek and destroy the invaders. Macrophages can be made more quickly by the body than the more specialized cells of the adaptive immune system, but they are not as effective or specialized [34].

Short-Lived Neutrophils

Neutrophils are another type of phagocyte. They were once called microphages by Elie Metchnikoff. Like macrophages, neutrophils are a product of haematopoietic stem cells in bone marrow, which produce myeloid cells. In addition to yielding the monocytes that become macrophages, myeloid cells also yield several other cells that make up the innate immune system, including neutrophils [30]. Unlike macrophages, neutrophils are very small, and they last only a few hours or days. They circulate in the blood only, while macrophages circulate in the blood and tissues. When macrophages respond to pathogens, they release chemicals into the blood stream, particularly cytokines, which alert the immune system to invaders. There are not enough macrophages to battle any infection alone, so neutrophils respond to the chemical alert and work in tandem with macrophages [30].

The lining of blood vessels is called the endothelium. Neutrophils are so tiny that they slip between the gaps separating endothelial cells, moving in and out of the blood vessels. Chemicals released by the macrophages after binding to a pathogen cause the neutrophils to bind more firmly to the endothelial cells. Once the neutrophils are securely bound to the endothelium, they squeeze their way into the interstitial fluid, and the endothelium dilates. The dilation makes it even more permeable than it was before the macrophages reacted to the pathogens, which allows some blood to flow into the tissues surrounding the blood vessels, making the area red, warm, painful and swollen. The process is known as the inflammatory response [35]. Sometimes bacteria release chemicals that guide the neutrophils toward them. The macrophages also release chemicals called chemokines that guide the neutrophils toward the site of infection. Like macrophages, neutrophils use phagocytosis to envelope and destroy the pathogens. Once completing this task, the neutrophils die. If there are enough dead neutrophils at an infection site, the dead cells forms the substance known as pus. Pus is a sign that the body is healing itself, and its color and consistency can alert a healthcare provider to the nature of the infection. Because neutrophils are so short-lived but so plentiful, they are especially important for fighting acute infections, such as an infected wound. Macrophages, on the other hand, are long-lived and are more useful for chronic infections [32].

Complement System

The complement system creates a bridge between the innate immune system and the adaptive immune system. It consists of approximately 20 proteins that are manufactured in the liver which spent most of their time circulating through the bloodstream in an inactive form. When they come into contact with PAMPs at infection sites they become activated, and once the complement system is activated, the proteins activate other proteins in a cascade. After the proteins activate, they join together to form a membrane-attack complex (MAC), which pushes across the cell membrane of infectious microbes, allowing fluids to flood into the pathogen and cause it to burst. In addition, the complement proteins bind directly to PAMPs, which tagged those allowing phagocytes to more easily identify the pathogens for destruction. The proteins also make it easier for antibodies to find the antigens when the adaptive immune system becomes involved [35].

Mycobacteria

Mycobacteria are most usually found as Bacilli, or rod-shaped bacteria. Their cell walls are surrounded by thick waxy coat, which protects them in harsh environments. Sometimes, they shed their cell wall. In this case they are known as the Spheroplast form of the bacteria [24]. Mycobacteria are extremely hardy. They are highly resistant to germicides, because of their thick protective cell wall. They are highly resistant to drying, and can exist outside the body without moisture for long periods [25]. The standard stain test for bacteria, the Gram Stain, does not work for mycobacteria, because their waxy coat will not take the dyes involved in the stain. A different staining method must be used, namely the Ziehl-Neelsen Stain, a method which removes the waxy coat with detergents before staining them [36]. This staining method works for the bacillus form of the bacteria, but does not work the spheroplast form. There is no known stain test for the spheroplast form of mycobacteria. To test for spheroplast form of these bacteria requires genetic testing, using the Polymerase Chain Reaction [37].

Pathogenesis of Mycobacteria

The number of mycobacteria required to establish an infection is extremely low. Mycobacterium tuberculosis, an obligate pathogen, can establish infection with as few as one to ten bacteria. Compare

this to the one hundred thousand bacteria required to establish a Salmonella infection. This indicates that the immune system can be very unsuccessful at combating these organisms. When pathogenic mycobacteria enter the body, they are very successful at evading the body defenses [38]. Their waxy coat helps to protect them against the high acidity of the stomach. The surfactant (soap-like) qualities of bile salts are not powerful enough to wash away their waxy coat. Also, they are not susceptible to the anti-biotic chemicals produced by the normal flora. Once at their preferred site of infection, pathogenic mycobacteria tend to allow themselves to be phagocytosed (swallowed) by Macrophages (white blood cells), within which they are able to resist destruction, and are able to multiply [39]. The host immune reaction to the organism varies widely between different individuals. Some individuals are able to control the infection, whereas others go on to develop a chronic infection. This latter group further breaks down into two groups depending on the type of immune response they mount [40].

Mycobacteria Mechanisms of Evading Phagocytes

The pathogenicity of *M. tuberculosis* is largely attributed to its ability to survive within macrophages by arresting phagosomal maturation [41]. This bacterium is exquisitely adapted to life within macrophages and not only arrests phagolysosome formation but can also escape the phagosome [42] and modulate other macrophage defences to promote its survival [43,44]. Phagosomal escape, a previously unappreciated facet of intracellular *M. tuberculosis*, requires the expression of a novel bacterial secretion system, ESX, which is lacking in avirulent mycobacteria [45]. Phagocytosis of *M. tuberculosis* by macrophages occurs through the engagement of various receptors, including CR3 [46]. However, unlike other particles that are engulfed by the same receptors, the *Mycobacterium*-containing phagosome fails to progress and become a phagolysosome and is instead arrested at an early stage [47]. Arrested *M. tuberculosis*-containing phagosomes are characterized by the presence of Rab5A, but the recruitment of Rab5A effectors, such as EEA1 and hvPS34, is impaired [47,48], and as a result, PI(3)P does not accumulate. *M. tuberculosis* uses a range of protein and lipid effectors to alter PI(3)P signalling [49,50]. The mycobacterial phosphoinositide lipoarabinomannan [49], a component of the cell wall that is shed from live bacteria and becomes distributed throughout the endocytic network [51], prevents the increase in cytosolic (Ca^{2+}) that normally accompanies phagocytosis and that is thought to be required to activate hvPS34 through calmodulin [49]. *M. tuberculosis* further impairs cytosolic (Ca^{2+}) flux by inhibiting sphingosine kinase, which converts sphingosine to sphingosine-1-phosphate, which in turn promotes (Ca^{2+}) efflux from the endoplasmic reticulum (ER) [52,53]. *M. tuberculosis* also produces the phosphatase SapM, which specifically hydrolyses PI(3)P [50]. This combined strategy effectively depletes PI(3)P from early phagosomes and prevents the transition to the late and phagolysosomal stages.

Activation of macrophages increases their ability to eradicate intracellular *M. tuberculosis* and other organisms [54,55]. This is highlighted by the observation that interferon-γ (IFnγ)-stimulated macrophages demonstrate enhanced bacterial clearance; in stimulated cells, *M. tuberculosis*-containing phagosomes are sequestered by autophagic compartments that ultimately fuse with lysosomes [56]. This autophagic response can be enhanced by Toll-like receptor ligands [57] and the activation of immunity-related p47 guanosine triphosphatase protein [58]. Immunity to pathogens such as mycobacteria is in part attributable to the activation of the inflammasome, a multiprotein complex that facilitates the killing of intra cellular bacteria and is required for interleukin-1β (Il-1β) processing. Il-1β enables macrophages to overcome the arrested maturation of the *M. tuberculosis*-containing phagosome [59,60] through an unknown mechanism that may involve restored PI(3)P production and subsequent maturation of the phagosome. Interestingly, the bacteria have also evolved a way to counteract the inflammatory response: *M. tuberculosis* secretes ZmpA, a predicted zinc metalloprotease that inhibits Il-1β processing by the host cells [60]. Intracellular survival of the bacteria therefore depends on an ongoing, multilevel tug of war between the pathogen and host macrophage.

Conclusion

Humans have two types of immune systems for protection against pathogens. One of the immune systems is called the innate immune system. The innate immune system is also present in most other life forms. In vertebrates, this system employs phagocytes as one of its lines of defense. Phagocytes are the soldiers of the immune system, and provide innate immunity.

They are responsible for swallowing, killing and digesting invading microbes by phagocytosis. When pathogenic organisms such as mycobacteria enter the body, they are very successful at evading the body defenses especially phagocytic action of phagocytes. This is done by adopting certain mechanisms such as arresting phagosomal maturation and secretion of ZmpA that inhibits Il-1β processing by the host cells.

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