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# A New perspective: How Pathogens Manipulate Phagocytosis?

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**ABSTRACT**

The immune system is a complicated, closely regulated mechanism that evolved to keep people healthy from infectious pathogens. Phagocytosis is important for both innate and acquired immunity, which is a critical process for microbial pathogens and apoptotic cells to be consumed and eliminated. However, several pathogens have evolved different strategies to escape detection and killing by phagocytosis. Recently, with the increase in infectious diseases and antibiotic resistance, it is significant for people to have a deep understanding of immune evasion, which may become an opportunity to explore new treatments and vaccination. Additionally, researchers mostly study immune evasion of a single pathogen but rarely summarize pathogens from the perspective of immune mechanisms. Here, we present the current understanding of phagocytosis and give a brief discussion of how pathogens control phagocytosis at different stages.

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## Introduction

There is a plethora of bacterial, fungal, and viral infections affecting various functions of the human body, specifically the phagocytosis process (1-4). Generally, phagocytosis begins with the recognition and ingestion of microbial pathogens larger than 0.5 pm into a vesicle generated from the plasma membrane called a phagosome (5, 6). This recognition is accomplished by using various receptors that recognize specific molecular patterns found in pathogenic microorganisms (7). Following that, these receptors initiate signaling cascades that result in phagocytosis and after the receptor contact, the plasma membrane surrounds the microorganism to be ingested and then shuts at the distal end, forming a vacuole into which the microorganism is internalized (Figure l) (8). This vacuole, the early phagosome, then merges with endocytic vesicles and simultaneously separates from secretory vesicles, changing it into a late phagosome (9). This dynamic mechanism, called "the kiss-and-run" paradigm, involves sequential fusion and fission events between the nascent phagosome and endosomes (10). Later on, the intermediary phagosome matures into a microbicidal vacuole called the phagolysosome by merging with lysosomes and altering its membrane and internal properties via a process called phagolysosome maturation (11). This process culminates in membrane modification, progressive acidity of the phagosome, and the establishment of an oxidative and degradative environment (12).

Phagocytosis is now known to have various functions in several cell types. Professional phagocytes help with innate immunity by removing harmful bacteria, fungi, and cancerous cells, and they also help with adaptive immunity by presenting antigens to lymphocytes (13). Phagocytosis functions as a link between innate and adaptive immunity. Therefore, many pathogens choose to manipulate phagocytosis to avoid detection and killing by the immune system, and they have successfully evolved numerous tactics to block and inhibit phagocytosis (14). Some previous reviews have already presented a comprehensive understanding of phagocytosis and immune evasion (15, 16). However, most of them start with a single pathogen rather than the immune system and the speed of research has not kept pace with microbial evolution (16). Moreover, there has been a lack of learning novel strategies in recent years. It is the purpose of this review to describe and update how various microbial pathogens obstruct phagocytosis in order to maintain their infection. This is a new perspective to help people better understand phagocytosis, which could help develop drugs and vaccines that target phagocytosis in the future. Some strategies include avoidance of pha-

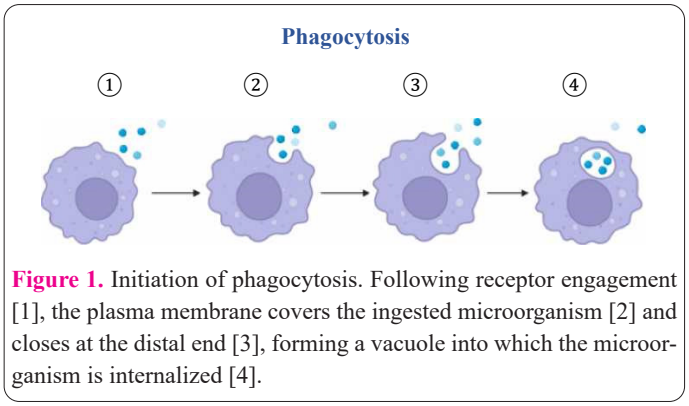


**Figure 1.** Initiation of phagocytosis. Following receptor engagement [1], the plasma membrane covers the ingested microorganism [2] and closes at the distal end [3], forming a vacuole into which the microorganism is internalized [4].

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gocytosis, preventing the formation of the phagosome, resistance to phagolysosome contents, and escape from the phagosome physically will be discussed.

**Avoidance of phagocytosis**

Pathogenic microorganisms, for the avoidance of phagocytosis, use the most effective method of escaping their destructive force to simply prevent ingestion (17). *Klebsiella pneumoniae* is an opportunistic pathogen that primarily affects immunocompromised patients (18), but a few serotypes (particularly K1 and K2) are highly invasive and can cause systemic infection in otherwise healthy individuals (19). Some *K. pneumoniae* have transcriptional regulators KP1_RS12260 (KbvR), which is a critical regulator involved in virulence and defense against macrophage phagocytosis. The transcriptome analysis and phenotype experiments revealed that deletion of kbvR reduced capsular polysaccharide (CPS) production and partially outer membrane protein biosynthesis (OMPs) (20). Thus, KbvR contributes to the bacterial defense against macrophage phagocytosis in *K. pneumoniae*. Additionally, the outer membrane (OM) that acts as a barrier in some gram-negative bacteria, preventing toxic compounds such as antibiotics and detergents from entering the cell (21). The folding and insertion of -barrel proteins into the OM are mediated by the -barrel assembly machinery (BAM) complex, which is composed of the integral membrane protein Ba mA (YaeT) and four accessory lipoproteins BamB (YfgL), BamC (NIpB), BamD (YfiO), and BamE (YfiE) (SmpA)? YfgL (BamB) is anchored to the periplasmic face of the OM (22, 23) and plays a role in *E. coli* and *Salmonella enterica* serovar Enteritidis membrane permeability and antibiotic resistance (24, 25). The yfgL mutation in *K.pneumoniae* increased susceptibility to vancomycin and erythromycin and is required for anti-phagocytosis and survival of bacteria in vivo (26).

Moreover, some bacteria can intoxicate phagocytes by producing special substances (27-29). *Staphylococcus aureus* can produce a variety of pore-forming protein toxins, all of which play a significant role in cell death and lysis (30, 31). These toxins mainly include leukocidin (32) and a-hemolysin (Figure2) (33). Leukocidins are dimer proteins, including LukAB, LukED HlgAb, and so on, which do not attack any membrane indiscriminately because they must first attach to certain membrane receptors; only cells that have these receptors get intoxicated (34). For instance, LukE interacts with the chemokine receptor CCR5 on macrophages, signalling the active leukocidin LukED to lyse these cells, which helps cell lysis. Another toxin from S. aureus, p-hemolysin, creates holes in macrophage membranes as well. It assembles into a -barrel pore of seven identical monomers across the cell membrane using the phagocyte protein ADAM 10 (a disintegrin and metalloproteinase domain-containing protein 10) as a receptor. Consequently, P-hemolysin helps the pathogen enter the host cells (35, 36).

Furthermore, pathogens have devised techniques to evade phagocytosis by preventing actin polymerization (37). The actin cytoskeleton is required to form a phagocytic cup and subsequent extension of membrane protrusions around the target particle (38). Additionally, all forms of phagocytosis involve the recruitment of F-actin beneath tethered particles and the re-arrangement of F-actin to facilitate engulfment, both of which are regulated by the Rho family GTPases (39). Therefore, some smart bacteria produce special toxins to control the GTPases, as they play an important role in actin energy. For instance, the bacterium *Clostridium difficile* is the causative agent of pseudomembranous colitis and is implicated in a significant number of cases of nosocomial antibiotic-associated diarrhea (40). The bacteria can produce glycosylating exotoxins A and B. Both toxins can influence the function of Rho, leading to a reduction of phagocyte cell migration and phagocytosis (41). Similarly, the bacterium *Photorhabdus asymbiotica* can produce a toxin (PaTox) that causes actin disorganization and restraint of phagocytosis (42).

**Prevent the Formation of the Phagosome**

Many pathogens develop their mechanisms directly to interfere with the maturation of phagosomes because they will face an unpleasant environment once they are ingested. (43-45). Different stages can be blocked in the process of phagosome formation by microbes, which include blocking acidification and inhibiting phagosome to lysosome fusion (46, 47).

One of the earliest characteristics of phagosome maturation is the phagosome's rapid and progressive acidification (48, 49). The number of V-ATPase molecules on the phagosome membrane rises as the phagosome matures. Some microorganisms just control the process to inhibit the maturation of the phagosome (50). For example, *M. tuberculosis* can secrete protein tyrosine phosphatase (PtpA), which plays a significant role in preventing the accumulation of V-ATPase on the phagosome membrane (51). Similarly, Gram-positive *Streptococcus pyogenes* inhibit V-ATPase action by expressing surface proteins controlled by the virulence factor Mga (47, 52). In addition, by eliminating the V-ATPase, the bacteria *Rhodococcus equi* and the dimorphic fungus *Histoplasma capsulatum* can also maintain a non-acidic phagosome (53).

Since the phagolysosome is the most toxic organelle for bacteria, many pathogens have developed methods to prevent lysosomes from fusing with the phagosome. The most well-known example is M. tuberculosis, which escapes lysosome fusion by preventing an early phagosome formation (54). Although the mechanism is complex, some key virulent factors were found to involve the process of impairing phagosome-lysosome fusion, such as lipoprotein LprG (26) and PtpA (55). Another mechanism by which *Mycobacterium tuberculosis* hinders phagosome-lysosome fusion is via inhibiting Rab7 recruitment and thereby autophagy-mediated destruction (56). Rab7 recruitment is required to mature mycobacteria-containing autophagosomes into autolysosomes, although this is inhibited by the virulence factor early secretory antigenic target-6 (ESAT-6) (53). How molecular events prevent phagosome-lysosome fusion is only partially known. However, the suppression of autophagosome-lysosome fusion (57) is performed via direct binding to Rab7 by another M. tuberculosis virulence factor called secretory acid phosphatase (SapM). It prevents Rab7 from participating in autophagosome-lysosome fusion by blocking Rab7's cytoplasmic domain (58).

Similarly, the Gram-negative bacteria *Coxiella burnetti* revise their phagosomes to focus the virulence factor Rab5 on the membrane and avoid lysosome fusion (59). Additionally, *S. pyogenes* can inhibit lysosome fusion by expressing the virulence component M1, which controls

vesicle trafficking (53). The fungus *A. fumigatus* (60) and the parasitic protozoa Leishmania (61) both appear to be capable of evading macrophages by blocking phagosome-lysosome fusion. In the instance of *A. fumigatus*, it has been shown that the chemical di hydroxy naphthalene-melanin on the pathogen's surface is responsible for modifying vesicle fusion events (62). For Leishmania, phagocytosis-mediated internalization of the promastigote is highly effective (61).

Pathogens not only hinder the production of phagolysosomes but also contain a variety of strategies for resisting the microbial components found in the phagolysosome lumen. Bera and his colleagues (63) found the first bacterial O-acetyltransferase (OatA) specific for peptidoglycans in *S. aureus* and showed that OatA is the molecular basis for staphylococci's high lysozyme resistance. As a result, this alteration of the molecule confers resistance on the peptidoglycan to the muramidase activity of lysozyme. In addition, S. aureus can inhibit the action of antimicrobial peptides. First, *S. aureus* can produce an exoprotein called staphylokinase which can bind with a-defensins. The a-defensins are peptides released by polymorphonuclear cells and guard against bacteria by disrupting their cell walls. The binding between staphylokinase and a-defensins will produce a complex formation. The biological result of this interaction is a near-complete suppression of α-defensins' bactericidal effect (64). Second, a novel staphylococcal gene, *mprF,* confers resistance to a variety of host defence peptides, including defensins and protegrins. This gene leads to a reduction in binding between antimicrobial peptides and bacteria (65). Third, the metalloprotease aeroly-

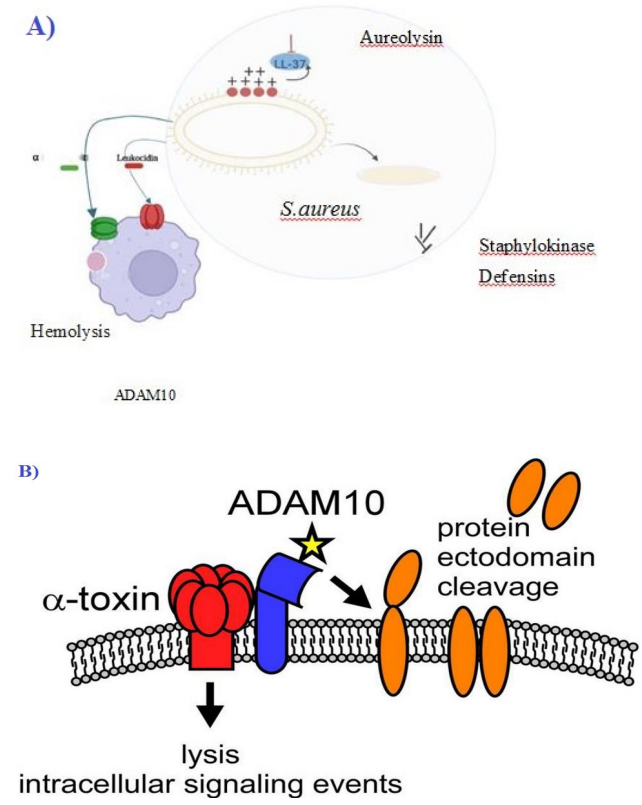


**Figure 2.** A) *S. aureus* produces toxins called leukocidins and hemolysins that increase membrane permeability by forming pores in the cell membrane. Additionally, it secretes staphylokinase and aureolysin to inhibit the activity of defensins and LL-37; B) Dual mechanism for the function of α-toxin (33).

sin is capable of degrading LL-37, a staphylococci-targeting peptide (66).

The oxidative environment created by the phagolysosome is likewise extremely harmful to the majority of bacteria. However, certain microorganisms have evolved strategies for combating the effects of reactive oxygen species (ROS) and reactive nitrogen species (RNS) (67). For example, at least two proteins have been identified that block the NADPH oxidase in M. tuberculosis, hence preventing the generation of ROS (68). The type I NADH dehydrogenase (NDH-1) inhibits ROS production and thus inhibits tumour necrosis factor-alpha (TNF-a) mediated host cell apoptosis, whereas the enhanced intracellular survival (eis) gene product (Eis) inhibits both ROS and proinflammatory cytokines production, resulting in apoptosis arrest. These effects appear to be dependent on the Eis protein's N-acetyltransferase domain (69). *M. tuberculosis* can also inhibit RNS by interfering with EBP50, a scaffolding protein that regulates iNOS migration to the membrane of macrophage phagosomes (70). Interestingly, overexpression of EBP50 greatly boosted iNOS expression and NO production, and EBP50-induced apoptosis is NO-dependent and mediated by Bax and caspase-3. Mycobacterium tuberculosis lowers and *Mycobacterium smegmatis* enhances EBP50 expression in RAW264.7 cells, implying that aggressive mycobacteria are capable of regulating macrophage antimycobacterial capabilities by reducing EBP50 expression and function (71).

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**Interest conflict**
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