Chapter

Functioning and Control of Phagocytosis

Laban Turyamuhika, Agaba Bosco, Asiimwe Moses, Musinguzi Benson and Okek Erick

Abstract

Phagocytosis is a very complex and versatile process that contributes to immunity through a series of events that is it's sometimes referred to the Come and Eat me process. Due to the recognition ingestion and digestion then destruction. It's also central to tissue homeostasis and remodeling by clearing dead cells. This ability of phagocytes to perform such diverse functions rests in large part on their vast repertoire of receptors. In this book chapter we looked at the processes used by phagocyte to perform there phagocytosis function. This is made possible by the binding of opsonins on the microbes like the C3b of the complement. This works as a chemo attractant to the phagocytes to come and initiate the process of eating. On recognition this microbe or dead cell interacts with the phagocyte with the help of a very big repertoire of receptors the microbe is engulfed with in the phagosome. As microbes interact with the phagocyte receptors a cascade of signaling events downstream that then activate phagocytosis. This membrane and cytoskeleton remodulation lead to the formation of pseudopods that cover the entire microbe forming a phagocytic cup which closes a few minutes to take up the microbe completely. The signal cascade is most known for the Fc receptor activities. Crosslinking of the Fc receptor on the surface of phagocyte activate phagocytosis and any other effector functions such as activation of the oxidative burst, degranulation, antibody dependent cell mediated cytotoxicity and activation of genes for cytokine/chemokine production that are beneficial in microbe destruction and initiation of inflammation. This starts once the interaction of phagocytes receptors and their ligands on the target microbes takes place appropriately. The phagocyte receptors will then aggregate to activate a series of pathways that regulate actin cytoskeleton which helps in the formation of a new vesicle which comes out of the membrane to enclose the microbe. In here a number of processes and stages take place all aimed at killing and denaturing the particle. They include early phagosome, intermediate phagosome, phagolysosome formation and the late phagosome all these participate in eliminating the phagocytized microbe. However with all the above phagocytic efficiency, some pathogens evade phagocytosis using different means and presence of certain capacities that facilitate evasion examples of organisms that evade phagocytosis include *Mycobacterium tuberculosis, Listeria monocytogens Escherichia coli* etc. all these use different means in evasion. Therefore the concept and science of Phagocytes used to be studied more to explore more pharmaceutical products based on the evasion mechanisms.

Keywords: phagocytes, recognition, internalization, degranulation, signaling evasion

1. Introduction

It's a century since a great discovery by Elie Metchnikoff which championed the role of phagocytosis in cellular immunity. Although some other group had observed the uptake of particles from simple to complex organisms he understood and stated better its significance in the host response to injury and infection. This made our understanding of inflammation and homeostasis much better, with more improved tools for cellular and molecular biology the study of the role of phagocytosis and its contribution to physiological and pathological processes, including receptor function in innate and acquired immunity.

2. Professional phagocytes

Neutrophils and macrophages both have a key role in innate immunity because they recognize ingest and destroy pathogens without the assistance of the adaptive immune response. Usually macrophages are the first to encounter microbes in the tissues but are soon replaced but a large number of neutrophils to sites of infection [1].

Our bodies are made of strong epithelial layers of defense however some pathogens have evolved strategies to penetrate these defense and therefore epithelia can be disrupted by wound, insect bites or abrasions that may lead to entry of pathogens.

Phagocytosis is fundamental for host defense against invading pathogens and contribute to the immune and inflammatory response. Phagocytosis is done majorly in specialized cells in multicellular organisms and is facilitated by a number of cells called phagocytes preferably professional phagocytes and these include neutrophils, macrophages, monocytes, dendritic cells. In this process a cell uses its plasma membrane to engulf a large particle giving rise to an internal compartment called the phagocytosis. Microbes are recognized by phagocytes that have a number of receptors on their surfaces which directly recognize conserved molecules on the microbe surfaces called PAMPs. This particulate matter must be opsonized (coated) with IgG, complement fragments C3b or iC3b, fibrinoctin or other proteins before being recognized and engulfed by PMNs. This process is essential for tissue balance and involve several steps that include particle recognition, particle ingestion early phagosome formation, late phagosome formation and phagolysosome formation [2].

3. Receptors involved in phagocytosis

Variety of ligands can be recognized by most phagocytic cells, with their efficient recognition requiring a great number of receptor types with distinct selectivity. Multiple receptor types are co expressed and this helps display a diverse array of adherent opsonins, some phagocytic receptors engaged in the process of phagocytosis may not be phagocytic receptors. The most commonly engaged receptors are listed in the **Table 1** [13]. Macrophages recognize and identify the phagocytic targets using this array of receptors that are normally displayed on the plasma membrane of microbes.

This happens through a coordinated signaling cascade that is initiated once a phagocytic receptor binds its ligand [14].

The recognition and identification were the first known functions of phagocytosis.

Receptor	Ligands	references
Pattern-recognition receptors		
Dectin-1	Polysaccharides of some yeast cells	[3]
Mannose receptor	Mannan	[4]
CD14	Lipopolysaccharide-binding protein	[5, 6]
Scavenger receptor A	Lipopolysaccharide, lipoteichoic acid	[6]
CD36	*Plasmodium falciparum*-infected erythrocytes	[7]
MARCO	Bacteria	[8]
Opsonic receptors		
FcγRI (CD64)	IgG1 = IgG3 > IgG4	[9]
FcγRIIa (CD32a)	IgG3 ≥ IgG1 = IgG2	[9]
FcγRIIIa (CD16a)	IgG	[9]
FcαRI (CD89)	IgA1, IgA2	[10]
FcεRI	IgE	[11]
CR1 (CD35)	Mannan-binding lectin, C1q, C4b, C3b	[12]

Table 1.
Shows human phagocytic receptors found on phagocytes.

4. Receptor synergy during phagocytosis

The engagement of apoptotic cells for example is achieved by action of CD36 that binds oxidized PS, and integrins that bind PS-bridging proteins, including MFG-E8. Signaling by integrins to the main actin cytoskeleton at sites of apoptotic corpse engagement involves Rac activation and completion of internalization which requires myosin [13]. The avidity of an interaction is normally thought of as the proportion pf the number of copies of a single receptor type engaged at a time. Therefor in the context of phagocytosis myriad different receptors exist and physiological targets expose a variety of ligands. This phenomenon raises the chances of combined avidity,

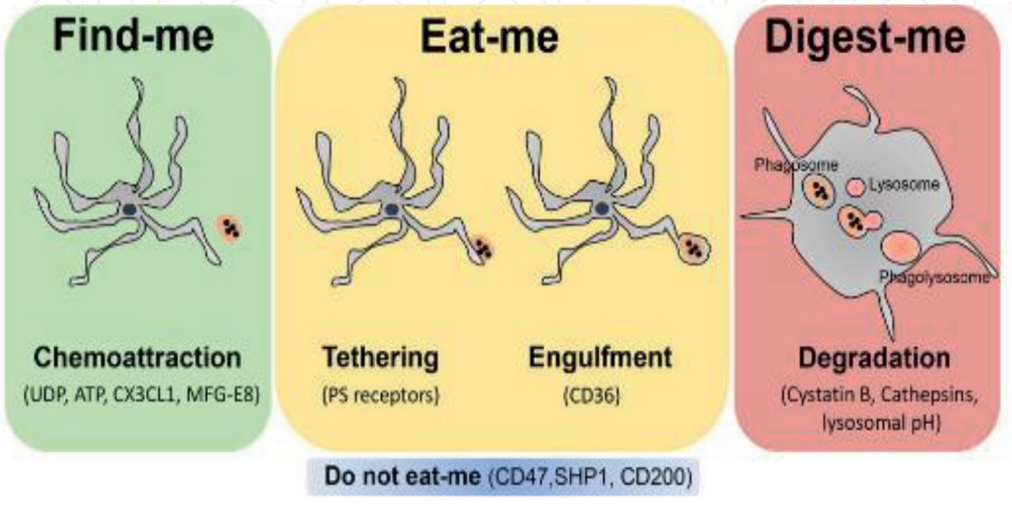

Figure 1.
The figure show the main steps of phagocytosis in dead cells and microbes.

conferred by simultaneous engagement of multiple unrelated receptor types. Thus a microbe exposed in serum is likely to be recognized immediately by pattern recognition receptors like Dectin (**Figure 1**) [15].

4.1 The Phagocytosis Process

These are the main steps that facilitate phagocytosis of microbes and dead cells. To what extent does the phagocyte decode the microbial genetics to be able to mount an appropriate response? There is a clue on the fact that there are cations like magnesium and calcium. These cations must be present in in the extracellular fluid in sufficient quantities for macrophages to ingest a variety of microbes with ease, however C3 opsonized particles are more easily ingested with a much lower divalent amounts of cations than unopsonised ones. Therefore C3 seem to have increase ingestion by potentiating the effect of cations [16].

5. The schematic shows the process of phagocytosis

IMAGE FROM Molecular and Cellular Immunology by Saunders 4th edition. page35. Pathogens could be ingested by different membrane receptors on the phagocytes. Some receptors bind microbes directly while others will only bind opsonized pathogens. But remember that the Mac-1 integrins binds microbes opsonized with complement protein e.g. C3. The pathogens are internalized in the phagosome which then fuse with lysosomes to form phagolysosomes. Where the microbes are killed by ROS and nitrogen intermediate enzymes. (NO, nitric oxide, ROS, reactive oxygen species).

5.1 Step one: recognition of the microbe

Neutrophils and other macrophages are always exposed to cells that they ignore but instead will specifically take on different microbes and particles. The specificity is due to the presence of different of receptors on these cells that recognize microbes [17]. Despite the various differences all phagocytic targets have a common characteristic that is they present the phagocyte multivalent arrays of ligands, a critical feature for the activation of most phagocytic receptors that are invariably activated by clustering laterally in the plane of the membrane therefore unlike GPCRs or growth factor receptors that undergo trans membrane remodulation upon binding with their ligands, phagocytic receptors are stimulated when their fluid cation quantities are elevated as they get immobilized by closely apposed stationary ligands [17]. Pathogen ligands for most phagocytic receptor include various protein receptor and complex lipids such as lipopolysaccharides, teichoic acids and mycobacterial lipids [18]. The none opsonic receptors that are expressed by professional phagocytes include lectin like recognition molecules such as CD169, CD33 and the related receptors specifically for sialylated membrane residues [19]. You recall that some receptors may bind these pathogen associated molecules) PAMPs (and still fail to initiate phagocytosis majorly due to poor preparation or priming. TLRs and some G-protein coupled receptors prime the cell for phagocytosis by inducing inverted activation of phagocytic integrins [20]. Phagocytes also express some other types of receptors like the Dectin-1 which for fungal betaglucan [21] with well-defined signaling capacity, other related lectin include MICL, Dectin 2,Mincle and DNGR-1 with other group of scavenger receptors like SR-A, MARCO and CD36 that have different domain structures which work by overlapping of recognition apoptotic [22].

5.2 Step two: particle internalization

When a particle binds with a phagocyte receptor, various signaling pathway events are triggered to activate phagocytosis. Most changes in membrane conformation and the actin cytoskeleton take place which leads to the formation of pseudopods that the engulf the microbe [23]. The Fcy receptors get activated in the plane of the phagocyte membrane when they aggregate after binding to their IgG ligands which then cover the particle to be ingested [24].

5.3 Step three: phagocyte formation

Signaling events are triggered to start phagocytosis immediately when the phagocyte receptors engage the microorganism. This is followed by membrane remodeling and the cytoskeleton leading to the formation of pseudopods that engulf the microbes. This causes lipids to associate and dissociate from the membrane of phagosome in orderly way [25]. A depression of the membrane (a phagocytic up) is made at the point of contact of the phagosome with the microbe, then the membrane protrusions fuse at the distal end to finally seal off the new phagosome [26, 27]. When the Fcy Receptors aggregate after binding to their IgG ligands that cover the particle to be ingested. Clustering of activating receptors FcyRs results in phosphorylation of the immunoreceptor tyrosine based activation motifs (ITAMs) present in the cytoplasmic domain of the receptors in the case of FcyRIIa and FcyRIIc or in an FcR common Y-chain [24, 28].

A number of receptors are attached on the phagocyte that cooperate to facilitate phagocytosis and ingestion. The interactions of receptors are improved with possible targets by (i) creating active protrusions that allow the cell to explore larger area increasing the chances for receptors to engage their ligands. (ii) selectively removing of the larger glycoproteins allowing the receptors to diffuse more freely on the membrane [29]. The phosphatase CD45 can extend more than 40 nm from the cell membrane [30] and it's a real obstacle for most phagocytic receptors, therefore removing these large molecules could drastically improve receptor binfding.CD45 was first identified during the Dectin 1 mediated phagocytosis in a phagocytic synapse [31] for its resemblance with the T lymphocyte immune synapse. When the T cell receptor TCR molecules on the T lymphocyte interact with the MHC molecules on an antigen presenting cell APC, a central cluster of engaged TCRs are surrounded by a ring of integrin LFA-1 molecules and CD45 is excluded from the center [32].

6. Phagosome maturation

The newly formed phagosome changes its membrane composition very fast to become a microbicial vacuole called the phagolysosome. The process used to transfer endocytosed material from endosomes to lysosome is complex and has been described hypothetically to explain the process of phagolysosome formation [33]. Phagosome maturation can be divided into three stages namely early phagosome late phagosome and phagosome.

7. Early phagosome

The newly formed phagosome rapidly gets the characteristics of the early endosome by fusing with sorting and recycling endosomes [34]. The interior becomes

acidic but not very destructive, the small GTPase Rab5 regulates the membrane fusion events between endosome and early endosome. This ATPase on the membrane is useful for the transition from the early to a late phagosome, Rab5 then works through the recruitment of EEA1 (early endosome antigen 1), that promotes the fusion of the new phagosome with early endosomes [35, 36]. Rab5 also recruits the classic PI-3 K human vacuolar protein-sorting 34, which then generates phosphatidylinostol3-phosphate [37]. The acidity of the early phagosome is activated by the recruitment of and action of V-ATPase accumulating on its membrane and also by accumulating on its membrane and also by transient fusions with more acidic vesicles. The V-ATPase Trans locates protons (H) lumen of the phagosome using cytosolic ATP as an energy source.

8. The late phagosome

Rab5 is lost as the phagosome matures and Rab7 appears on the membrane which mediates the fusion of the phagosome with late endosomes [38]. Similarly proteins that will be recycled are separated through sorting of vesicles whereas the proteins intended for degradation are eliminated in intraluminal vesicles and dare directed into the lumen of the phagosome [39], which will make it a little acidic due to the

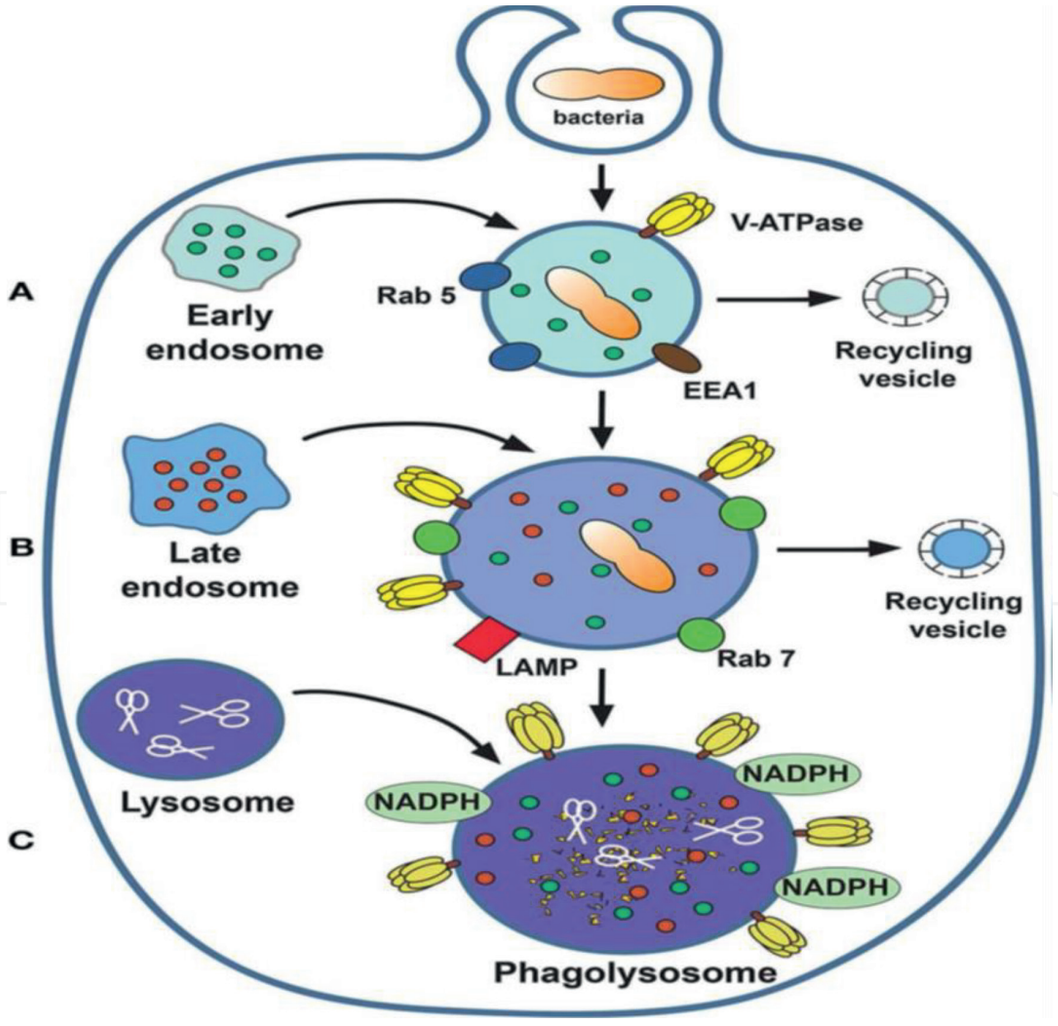

Figure 2.
The phagolysosome.

action of V-ATPase molecules on the membrane [40]. The lysosomal associated membrane proteins (LAMPS) and luminal proteases cathepsins and hydrolases) are incorporated from fusion with late endosomes or from the Golgi apparatus [41]. This well-illustrated in the **Figure 2**.

To mature to phagolysosomes these late phagosome fuse with lysosomes, which are the definitive microbicial organelles [42, 43]. Phagolysosomes have many sophisticated mechanisms that eliminate and degrade microorganism. They usually contain degradative enzymes like proteases, lysozymes, lipases and cathepsins, they are also acidic (ph. 5–5.5), due to the presence of V-ATPase molecules on their membrane [44]. This phagolysosome also presents with NADPH oxidase responsible for producing reactive oxygen species that are bactericidal like the superoxide (02-) [45] superoxide dismutase to H2O2 that can react Cl- ions to form hypochlorous acid, a very potential microbicial substance. This final reaction is catalyze by enzyme myeloperoxidase [46]. The best anti microbicial agent of neutrophils is hydrogen peroxide despite it being bactericidal, in its own way it can be anti-fungal and antiviral using myeloperoxidase in presence of hyalide ions [47].

9. Strategies pathogens use to evade phagocytosis

The importance of phagocytosis cannot be under scored in the prevention and clearance of infection and its because of this that mic robes have devised different means to dodge recognition and eventually phagocytosis **Table 2.**

Mostly the microbes interfere with opsonins binding of polysaccharide-based capsules which shield the deposition of opsonins, while other bacteria express some surface proteins that inhibit binding for example Group A streptococci escape complement mediated phagocytosis using M proteins that are lacking in higher organisms [48]. These PAMPs are usually detected by receptors on the phagocyte particularly Toll like receptors. fc and complement receptors are the best studied receptors and there signaling is quite known more phagocytic receptors studies are ongoing.

Effectors	**Importance**	**Species involved**
Protein A	Binds Fc region, preventing normal interaction with FcyR	*Cryptococcus aureus*
Capsule	Prevents complement deposition	*Cryptococcus neoformans,streptococcus pneumonia,Eschericia coli KI,Klebsiela pneumonia,Neiseria meningitides,S,aureus Haemopholus influenza Treponema pallidium*
M proteins	Prevents binding to CRs	*Streptococcus pyogens*
YadA	Prevents deposition of C3b	*Yersinia entercolitica*
Organisms that inhibit signaling		
YopE	GAP for RhoA,Rac and CDC42	*Yersinia sp.*
ExoT	Cysteine protease of Rho,Rac and Cdc42	*Yersinia sp.*
YOPH	Tyrosin phosphatase for Cas,Fyb,SKAP,-HOM,paxillin and FAK	*YERSINIA SP.*

Effectors	Importance	Species involved
Espj	Inhibits FcyR and CR3 mediated phagocytosis	*Eschericia coli*
EspB	Inhibits myosin actin interactions	*Eschericia coli*
EspH	Inactivates Rho GEFs	*Eschericia coli*.
T4SS	Delays phagocytosis	*Helicobacter pyroli*
Nef	Inhibits membrane delivery to the phagosome	*HIV*

Abbreviations: CR, complement receptor, GAP, GTPase-activating proteins, GEF, guanine nucleotide exchange factor, HIV, human immunodeficiency virus, T4SS, type 4 secretion system.

Table 2.
Shows different virulent factors microbes use to dodge uptake by phagocytosis.

10. Efficiency of phagocytosis

Many phagocytes have a relatively low phagocytosis capacity at rest and when inflammation gets in, phagocytes get exposed to a variety of activating stimuli which increase the efficiency of the cell to phagocytose. The activating stimuli include, bacterial products, cytokines and inflammatory mediators, the signals induced by these substances lead to increased activation of molecules involved I phagocytosis e.g. leukotrieneB4 increases Syk activation and consequently antibody dependent phagocytosis [49]. Also the action of P13K and ERK, which are essential enzymes for bacterial peptide, glanulocyte colony stimulating factor, leukotrienes and cytokines such as interleukin [50]. Phagocytosis can be regulated by cell differentiation, e.g. monocytes have lower phagocytic capability than neutrophils and macrophages, however they can enhance their phagocytic capacity after cell differentiation [51]. The capacity of monocytes to phagocytose diverse targets alter with the state of differentiation. Therefore during monocyte to macrophage differentiation the e most important signaling enzymes are reorganized in order to achieve increased phagocytosis [51, 52].

Functioning and Control of Phagocytosis
DOI: http://dx.doi.org/10.5772/intechopen.110511

Author details

Laban Turyamuhika[1*], Agaba Bosco[2], Asiimwe Moses[3], Musinguzi Benson[4] and Okek Erick[5]

1 Makerere University, Uganda

2 Malaria Control Programme, Ministry of Health, Uganda

3 Mountains of the Moon University, Fort Portal, Uganda

4 Muni University, Arua, Uganda

5 Uganda Virus Research Institute, Entebbe, Uganda

*Address all correspondence to: labanturyamuhika74@gmail.com

References

[1] Murphy K, Weaver C. Janeway's Immunobiology. USA: Garland Science, Havard Medical School; 2016

[2] Seeberg JC, Loibl M, Moser F, Schwegler M, Büttner-Herold M, Daniel C, et al. Non-professional phagocytosis: A general feature of normal tissue cells. Scientific Reports. 2019;**9**(1):1-8

[3] Herre J, Marshall AS, Caron E, Edwards AD, Williams DL, Schweighoffer E, et al. Dectin-1 uses novel mechanisms for yeast phagocytosis in macrophages. Blood. 2004;**104**(13):4038-4045

[4] Ezekowitz R, Sastry K, Bailly P, Warner A. Molecular characterization of the human macrophage mannose receptor: Demonstration of multiple carbohydrate recognition-like domains and phagocytosis of yeasts in Cos-1 cells. The Journal of Experimental Medicine. 1990;**172**(6):1785-1794

[5] Schiff DE, Kline L, Soldau K, Lee J, Pugin J, Tobias PS, et al. Phagocytosis of gram-negative bacteria by a unique CD14-dependent mechanism. Journal of Leukocyte Biology. 1997;**62**(6):786-794

[6] Peiser L, Makepeace K, Plüddemann A, Savino S, Wright JC, Pizza M, et al. Identification of Neisseria meningitidis nonlipopolysaccharide ligands for class a macrophage scavenger receptor by using a novel assay. Infection and Immunity. 2006;**74**(9):5191-5199

[7] Patel SN, Serghides L, Smith TG, Febbraio M, Silverstein RL, Kurtz TW, et al. CD36 mediates the phagocytosis of plasmodium falciparum–infected erythrocytes by rodent macrophages. The Journal of Infectious Diseases. 2004;**189**(2):204-213

[8] van der Laan LJ, Döpp EA, Haworth R, Pikkarainen T, Kangas M, Elomaa O, et al. Regulation and functional involvement of macrophage scavenger receptor MARCO in clearance of bacteria in vivo. The Journal of Immunology. 1999;**162**(2):939-947

[9] Anderson CL, Shen L, Eicher DM, Wewers MD, Gill JK. Phagocytosis mediated by three distinct fc gamma receptor classes on human leukocytes. The Journal of Experimental Medicine. 1990;**171**(4):1333-1345

[10] Bakema J, Van Egmond M. The human immunoglobulin a fc receptor FcαRI: A multifaceted regulator of mucosal immunity. Mucosal Immunology. 2011;**4**(6):612-624

[11] Daëron M, Malbec O, Bonnerot C, Latour S, Segal DM, Fridman WH. Tyrosine-containing activation motif-dependent phagocytosis in mast cells. Journal of Immunology (Baltimore, Md: 1950). 1994;**152**(2):783-792

[12] Ghiran I, Barbashov SF, Klickstein LB, Tas SW, Jensenius JC, Nicholson-Weller A. Complement receptor 1/CD35 is a receptor for mannan-binding lectin. The Journal of Experimental Medicine. 2000;**192**(12):1797-1808

[13] Freeman SA, Grinstein S. Phagocytosis: Receptors, signal integration, and the cytoskeleton. Immunological Reviews. 2014;**262**(1):193-215

[14] Joffe AM, Bakalar MH, Fletcher DA. Macrophage phagocytosis assay with reconstituted target particles. Nature Protocols. 2020;**15**(7):2230-2246

[15] Miyanishi M, Tada K, Koike M, Uchiyama Y, Kitamura T, Nagata S. Identification of Tim4 as a phosphatidylserine receptor. Nature. 2007;**450**(7168):435-439

[16] Stossel TP. Phagocytosis. New England Journal of Medicine. 1974;**290**(14):774-780

[17] Abbas AK, Lichtman AH, Pober JS. Cellular and Molecular Immunology. san Francisco California: Saunders; 1991

[18] Wilson GJ, Marakalala MJ, Hoving JC, Van Laarhoven A, Drummond RA, Kerscher B, et al. The C-type lectin receptor CLECSF8/CLEC4D is a key component of anti-mycobacterial immunity. Cell Host & Microbe. 2015;**17**(2):252-259

[19] Levine AP, Segal AW. What is wrong with granulocytes in inflammatory bowel diseases? Digestive Diseases. 2013;**31**(3-4):321-327

[20] Rosales C, Uribe-Querol E. Phagocytosis: A fundamental process in immunity. BioMed Research International. 2017;**2017**:23-32

[21] Drummond RA, Dambuza IM, Vautier S, Taylor JA, Reid DM, Bain CC, et al. CD4+ T-cell survival in the GI tract requires dectin-1 during fungal infection. Mucosal Immunology. 2016;**9**(2):492-502

[22] Gordon S. Phagocytosis: An immunobiologic process. Immunity. 2016;**44**(3):463-475

[23] Rosales C. Molecular Mechanisms of Phagocytosis. calos Rosales Mexico city: Springer; 2005

[24] Dale B. Enhanced Fcγ receptor signaling in Cbl-/-macrophages reveals surprising insights into the mechanism of phagocytosis. Columbia University; 2008

[25] Uribe-Querol E, Rosales C. Control of phagocytosis by microbial pathogens. Frontiers in immunology. 2017;**8**:1368

[26] Araki N, Hatae T, Furukawa A, Swanson JA. Phosphoinositide-3-kinase-independent contractile activities associated with Fcγ-receptor-mediated phagocytosis and macropinocytosis in macrophages. Journal of cell science. 2003;**116**(2):247-257

[27] Dart AE, Tollis S, Bright MD, Frankel G, Endres RG. The motor protein myosin 1G functions in FcγR-mediated phagocytosis. Journal of cell science. 2012;**125**(24):6020-6029

[28] Rosales C, Uribe-Querol E. Antibody-fc receptor interactions in antimicrobial functions. Current Immunology Reviews. 2013;**9**(1):44-55

[29] Freeman SA, Goyette J, Furuya W, Woods EC, Bertozzi CR, Bergmeier W, et al. Integrins form an expanding diffusional barrier that coordinates phagocytosis. Cell. 2016;**164**(1-2):128-140

[30] Chang VT, Fernandes RA, Ganzinger KA, Lee SF, Siebold C, McColl J, et al. Initiation of T cell signaling by CD45 segregation at'close contacts'. Nature Immunology. 2016;**17**(5):574-582

[31] Goodridge HS, Reyes CN, Becker CA, Katsumoto TR, Ma J, Wolf AJ, et al. Activation of the innate immune receptor Dectin-1 upon formation of a 'phagocytic synapse'. Nature. 2011;**472**(7344):471-475

[32] Dustin ML. Signaling at neuro/immune synapses. The Journal of Clinical Investigation. 2012;**122**(4):1149-1155

[33] Luzio JP, Pryor PR, Bright NA. Lysosomes: Fusion and function. Nature reviews Molecular Cell Biology. 2007;**8**(8):622-632

[34] Levin R, Grinstein S, Canton J. The life cycle of phagosomes: Formation, maturation, and resolution. Immunological Reviews. 2016;**273**(1):156-179

[35] Gutierrez M. Functional role (s) of phagosomal Rab GTPases. Small GTPases. 2013;**4**:148-158

[36] Kitano M, Nakaya M, Nakamura T, Nagata S, Matsuda M. Imaging of Rab5 activity identifies essential regulators for phagosome maturation. Nature. 2008;**453**(7192):241-245

[37] Vieira OV, Botelho RJ, Rameh L, Brachmann SM, Matsuo T, Davidson HW, et al. Distinct roles of class I and class III phosphatidylinositol 3-kinases in phagosome formation and maturation. The Journal of Cell Biology. 2001;**155**(1):19-26

[38] Rink J, Ghigo E, Kalaidzidis Y, Zerial M. Rab conversion as a mechanism of progression from early to late endosomes. Cell. 2005;**122**(5):735-749

[39] Hanson PI, Roth R, Lin Y, Heuser JE. Plasma membrane deformation by circular arrays of ESCRT-III protein filaments. The Journal of Cell Biology. 2008;**180**(2):389-402

[40] Kinchen JM, Ravichandran KS. Phagosome maturation: Going through the acid test. Nature Reviews Molecular Cell Biology. 2008;**9**(10):781-795

[41] Canton J. Phagosome maturation in polarized macrophages. Journal of Leukocyte Biology. 2014;**96**(5):729-738

[42] Pryor PR, Luzio JP. Delivery of endocytosed membrane proteins to the lysosome. Biochimica et Biophysica Acta (BBA)-molecular. Cell Research. 2009;**1793**(4):615-624

[43] Bright NA, Gratian MJ, Luzio JP. Endocytic delivery to lysosomes mediated by concurrent fusion and kissing events in living cells. Current Biology. 2005;**15**(4):360-365

[44] Marshansky V, Futai M. The V-type H+-ATPase in vesicular trafficking: Targeting, regulation and function. Current Opinion in Cell Biology. 2008;**20**(4):415-426

[45] Minakami R, Sumimoto H. Phagocytosis-coupled activation of the superoxide-producing phagocyte oxidase, a member of the NADPH oxidase (nox) family. International Journal of Hematology. 2006;**84**(3):193-198

[46] Nauseef WM. Myeloperoxidase in human neutrophil host defence. Cellular Microbiology. 2014;**16**(8):1146-1155

[47] Klebanoff S, Rosen H. The role of myeloperoxidase in the microbicidal activity of polymorphonuclear leukocytes. Oxygen Free Radicals and Tissue Damage. 1978:263-284

[48] Flannagan RS, Jaumouillé V, Grinstein S. The cell biology of phagocytosis. Annual Review of Pathology: Mechanisms of Disease. 2012;**7**:61-98

[49] Wang J-P, Chang L-C, Lin Y-L, Hsu M-F, Chang C-Y, Huang L-J, et al. Investigation of the cellular mechanism of inhibition of formyl-methionyl-leucyl-phenylalanine-induced superoxide anion generation in rat neutrophils by 2-benzyloxybenzaldehyde. Biochemical Pharmacology. 2003;**65**(7):1043-1051

[50] Knall C, Worthen GS, Johnson GL. Interleukin 8-stimulated

phosphatidylinositol-3-kinase activity regulates the migration of human neutrophils independent of extracellular signal-regulated kinase and p38 mitogen-activated protein kinases. Proceedings of the National Academy of Sciences. 1997;**94**(7):3052-3057

[51] Newman SL, Tucci MA. Regulation of human monocyte/macrophage function by extracellular matrix. Adherence of monocytes to collagen matrices enhances phagocytosis of opsonized bacteria by activation of complement receptors and enhancement of fc receptor function. The Journal of clinical investigation. 1990;**86**(3):703-714

[52] Kambayashi T, Koretzky GA. Proximal signaling events in FcεRI-mediated mast cell activation. Journal of Allergy and Clinical Immunology. 2007;**119**(3):544-552