Chapter

Non-myeloid Cell Phagocytosis

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Abstract

As professional phagocytes, myeloid cells, including macrophages, dendritic cells, and neutrophils, are often the targets for investigation and analysis of phagocytosis. Phagocytosis, however, has also been observed in nonmyeloid cells, including epithelium, mesenchymal, and smooth muscle cells. Colloquially known as nonprofessional phagocytes, these nonmyeloid cells are capable of phagocytosis of pathogenic material and efferocytosis of apoptotic bodies. Cells, such as those found in the epithelium, are often the primary site for viral and bacterial infection and have evolved to possess strong anti-pathogenic machinery of their own. The processes by which nonmyeloid cells can engage in phagocytic functions have wide implications for tissue homeostasis and disease pathogenesis, including infection and colonization. This chapter will review the phagocytosis capabilities in these nonmyeloid cells.

Keywords: efferocytosis, epithelial cells, internalization, barrier, nonprofessional, opsonization, trigger phagocytosis, zipper phagocytosis

1. Introduction

As professional phagocytes, myeloid cells, including neutrophils, macrophages, monocytes, mast cells, and dendritic cells, are actively recruited to sites of tissue damage, infection, and inflammation playing a key role in host defense [1]. Of these, neutrophils and macrophages are perhaps the most widely studied in terms of their roles in phagocytosis [2–4]. However, there is increasing evidence that nonmyeloid cells, including epithelial [5, 6] endothelial [7–9], mesenchymal [7, 10–12], and smooth muscle cells [13–16], can also engage in phagocytosis, or phagocytic-like mechanisms when phagocytosis is not their principal function. Phagocytosis by nonprofessional phagocytes is often referred to as internalization or even cannibalism, especially in the case of efferocytosis of apoptotic neighboring cells [17]. Nonprofessional phagocytes were first distinguished from professional phagocytes as early as 1970 after Rabinovitch demonstrated particulate uptake in fibroblasts [18, 19], although reports had demonstrated particulate uptake in nonmyeloid cells almost 40 years prior [20]. Since this initial observation, many nonprofessional phagocytes have been identified to have the phagocytic capacity and the capacity to clear potentially dangerous pathogens [21]. **Table 1** includes a summary of these cell types and the roles that they have been observed to play in phagocytosis. Compared to professional phagocytes, nonmyeloid cells engage in distinctively different

Nonmyeloid cell	Cell subtype	Phagocytosis	Key findings	Ref'
Epithelial	Hu. respiratory	Pathogen clearance	*P.aeruginosa* internalization is independent of CFTR expression.	[22]
	Hu. bladder, lung, ileocecal	Pathogen clearance	Involvement of an N-glycosylated protein receptor required for internalization.	[23]
	Hu. T84 monkey kidney	Pathogen clearance	Ineffective phagolysosome maturation in epithelium.	[24]
	MDCK, Hu. 16HBE14o-	Pathogen clearance *via* efferocytosis	*P.aeruginosa* internalized *via* efferocytosis of apoptotic cells.	[25]
	Hu. A549	Pathogen clearance	Containment of pathogen colonization by epithelium.	[26]
	Hu. A549	Pathogen clearance	Less efficient than professional phagocytes.	[27]
	CHO cells	Pathogen clearance	Heparin/Heparan-dependent internalization of pathogen.	[28]
	Ms. mammary	Efferocytosis	Receptor mediated engulfment *via* PSR, CD36, vitronectin receptor alpha vbeta3, and CD91.	[29]
	Hu. BEAS-2B Ms. HBEC Ms. MLE-12	Efferocytosis	Uptake induces anti-inflammatory cytokine release *via* Rac1.	[30]
	Hu. Thymus	Efferocytosis	Uptake relies on PSR and SR-B1.	[31]
	Rt. bladder	Efferocytosis	Epithelial clearance of erythrocytes	[32]
	Hu. hepatic biliary	Efferocytosis	PSR-mediated clearance results in chemokine increase.	[33]
	Hu. A549	Efferocytosis	Receptor-mediated recognition of apoptotic bodies.	[34]
	Rt. Kidney	Efferocytosis	KIM-1 recognition internalizes apoptotic bodies.	[35]
	CHO cells	Efferocytosis	LOX-1 recognition of apoptotic bodies.	[36]
	Ms. retinal pigment	Efferocytosis	Role of ABCF1 recognition in apoptotic bodies.	[37]
	Ms. HBEC	Efferocytosis	Efferocytosis by epithelium avoids IL-33-mediated inflammation.	[38]
	Hu. ARPE-19	Efferocytosis	Increased efficiency over macrophages in apoptotic clearance.	[39]
	Ms. follicular	Efferocytosis	Clearance of apoptotic neighboring cells.	[40]
	Ms. colonic	Efferocytosis	Role for BAI-1 mediated uptake in controlling inflammation.	[41]
	Ms. retinal	Phagocytosis (Photo receptor material)	Gas6 & Protein S ligands for TAM-mediated phagocytosis.	[42]

Nonmyeloid cell	Cell subtype	Phagocytosis	Key findings	Ref'
Endothelial	Hu. vascular	Pathogen clearance	Rho kinase in endothelial cells bind listeria and internalization mediated by formins.	[43]
	Ms. Hepatic sinusoidal	Efferocytosis	IL-1 enhanced scavenging of apoptotic bodies.	[44]
	Ms. Endothelium	Efferocytosis	SCARF1 mediated clearance of apoptotic bodies.	[45]
	Bovine Aortic	Efferocytosis	LOX-1 recognition of apoptotic bodies.	[36]
	Hu. umbilical vein	Phagocytosis platelet clearance	PS recognition on platelets-mediated phagocytosis.	[46]
	Ms. (brain) microvascular	Phagocytosis myelin clearance	IgG opsonization is required for endothelial cell clearance, inducing endothelial-mesenchymal transition.	[47]
Mesenchymal	Hu. MRC5 cells	Pathogen clearance	Actin-dependent uptake. LAMP-1 mediated phagolysosome maturation.	[27]
	Hamster embryonic fibroblasts	Pathogen clearance Efferocytosis	ConA-dependent zipper phagocytosis.	[48]
	Ms. ESCs	Efferocytosis	Inefficient (relative to macrophages) but effective clearance of apoptotic bodies.	[11]
	Hu. BM-MSCs	Efferocytosis	Observation of mesenchymal stem cell efferocytosis enhancing inflammation.	[10]
Smooth muscle	Hu. vascular	Efferocytosis	PS-PSR mediated phagocytosis.	[16]
	Pigeon vascular	Phagocytosis (cholesterol)	First identification of smooth muscle cell-derived foam cells.	[49]
	Ms. aortic	Phagocytosis (cholesterol)	Smooth muscle cells differentiate to a macrophage phenotype after cholesterol loading.	[50]
Hepatic	Hu. primary Stellate cells Hu. Hep G2 cells	Efferocytosis	Apoptotic clearance causes fibrogenic response.	[51]
	Rt. hepatocytes	Phagocytosis (lecithin-coated particles)	Exogenous substance uptake by hepatocytes.	[52]

Nonmyeloid cell	Cell subtype	Phagocytosis	Key findings	Ref'
Other	Rt. Sertoli cells	Efferocytosis	PS mediated clearance.	[53]
	Hu. Mesangial Kidney	Efferocytosis	CD36 independent clearance of apoptotic bodies.	[54]
	Ms. neuronal progenitor	Efferocytosis	Identifies neuronal precursors as nonprofessional phagocyte.	[55]
	Rt. chondrocytes	Phagocytosis (cartilage fragments)	CD163+ chondrocytes have phagocytic role in arthritis.	[56]

Hu.: Human, CFTR: Cystic Fibrosis Transmembrane Conductance Regulator, Ms.: Mouse, PSR: Phosphatidylserine Receptor, CD: Cluster of Differentiation, HBEC: Human Bronchial Epithelial Cells, Rac1: Ras-related C3 botulinum toxin substrate 1, SR-B1: The scavenger receptor, class B type 1, Rt.: Rat, KIM-1: Kidney Injury Molecule-1, LOX-1: lectin-like oxLDL [oxidized low-density lipoprotein] receptor 1, ABCF1: ATP-binding cassette sub-family F member 1, IL: Interleukin, BAI-1: Brain-specific angiogenesis inhibitor, Gas6: Growth arrest-specific 6, SCARF1: Scavenger receptor class F member 1, IgG: Immunoglobulin G, LAMP-1: Lysosomal-associated membrane protein 1, PS: Phosphatidylserine, ESCs: Embryonic Stem Cells, BM-MSCs: Bone Marrow Mesenchymal Stem Cells.

Table 1.
Key studies in nonmyeloid cell phagocytosis.

mechanisms to recognize, engulf, and destroy pathogens through phagocytosis. Nonprofessional phagocytes are demonstrably less efficient and lack factors such as Pattern Recognition Receptors (PRRs) capable of recognizing Pathogen Associated Molecular Patterns (PAMPs), as well as reactive oxygen species (ROS) and degradation enzymes required for effective clearance and degradation [19]. Nonmyeloid cells, however, provide a significant contribution toward the clearance of exogenous pathogens, cellular debris, and apoptotic bodies *via* phagocytosis, and what they lack in efficiency, can make up for in cell number [5, 57]. This chapter will focus on the specific functions of nonprofessional phagocytes, highlighting their differences from professional phagocytes and their specific and important contribution to tissue homeostasis.

2. Pathogen-induced phagocytosis

The active role of the host cell in the process of pathogen internalization, involving cytoskeletal rearrangements after pathogen recognition, ultimately distinguishes nonprofessional phagocytosis from infection [7, 19, 57]. There may be a few exceptions to this rule, such as Rotaviruses, known to gain infectious entry into the cell using the zipper mechanism, described below [58]. Internalization of the pathogen is, however, only the initial stage in the bigger mechanism of phagocytosis. The pathogen-containing internalized vesicle, otherwise known as the early phagosome, requires subsequent fusion with lysosomes in order to achieve pathogen killing [59]. The early phagosome matures by fusion with internal endocytic vesicles [59], recruiting factors, such as Rab5 [60], a small GTPase important for the maturation of the phagosome, and early endosome antigen 1 (EEA1) [61]. Rab5 remains transiently expressed in the early phagosome, directing the fusion of early endosomes [62, 63]. The schematic in **Figure 1** depicts the process of endosome formation, maturation, and role of Rab proteins in phagocytosis. Rab5 has been extensively studied and understood in myeloid cells during professional phagocytosis and has also been shown to be constitutively expressed in nonmyeloid cells, including epithelial cells [64–66], fibroblasts [66], and smooth muscle cells [67], controlling the phagocytic processes. Rab5 is considered a master regulator of early endosome formation and trafficking to the early phagosome. Rab5 expressing early phagosomes initiates the process of pathogen killing or apoptotic recycling by creating a mildly acidic microenvironment (pH 6.1) within the phagosome and engaging in relatively low levels of hydrolysis [68]. Rab conversion is a term used to convey phagosome maturation beyond the early phagosome. Maturation involves the recruitment of Rab7, functionally replacing Rab5 in the phagosome [69]. Rab7, like Rab5, is a member of the GTPase family that manages the maturation of phagosomes and recruits other factors, such as the RAB7 interacting lysosomal protein (RILP), necessary for later phagosome fusion with lysosomes [70]. Formation of a late-stage phagosome also requires the recruitment of Lysosomal-Associated Membrane Process-1(LAMP-1), necessary for lysosomal fusion [27, 71] Rab7 functionally interacts with RILP [70, 72], resulting in lysosomal fusion with the late-stage phagosome. Consequently, the phagolysosome structure is formed, creating a more acidic environment (pH 5.5) and generating a cocktail of degradation enzymes and ROS in effort to kill invading pathogens or break down apoptotic bodies [57]. While the process leading to the formation of the phagolysosome is similar, the recognition of the pathogen by nonmyeloid cells and internalization can occur through one of several known pathways. These pathways,

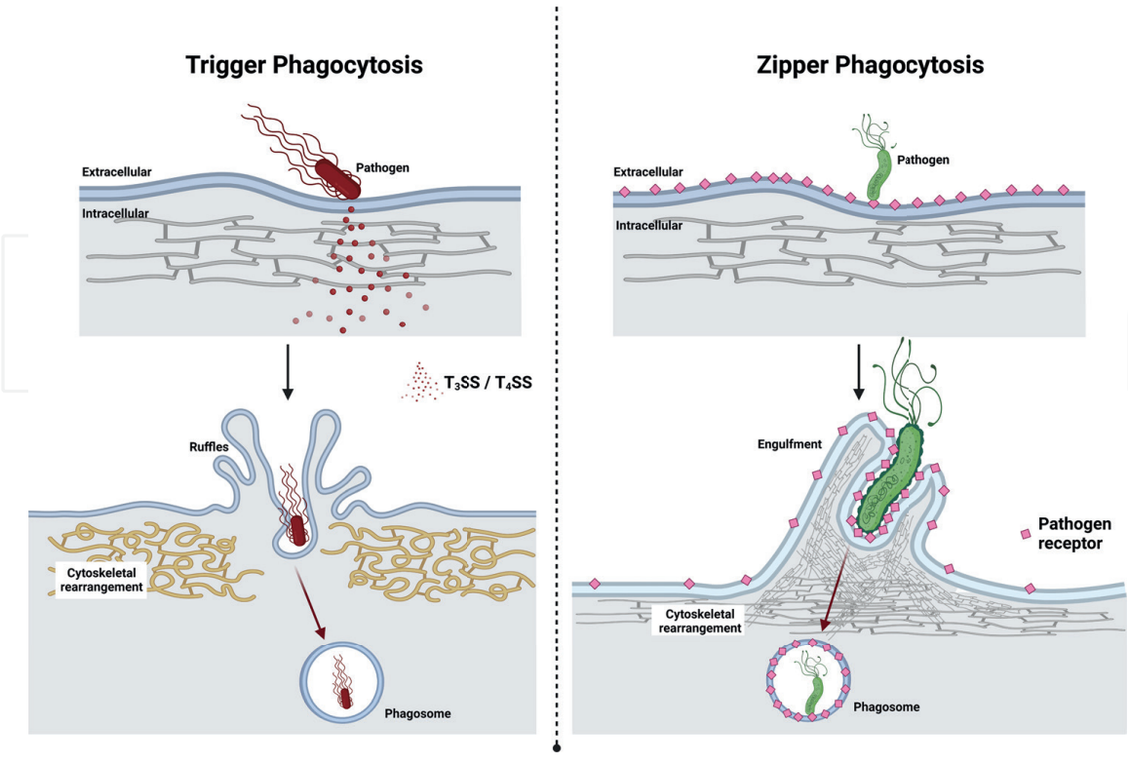

Figure 1.
Internalization models for pathogen-induced phagocytosis. For nonprofessional phagocytes, phagocytosis is induced by the pathogen. Two primary models are proposed: 1) trigger phagocytosis, caused when type 3 / type 4 secretion systems (T_3SS/T_4SS) cause cytoskeletal rearrangement, resulting in "ruffles" of the host cell membrane that engulfs and internalizes the pathogen and 2) zipper phagocytosis where the pathogen engages with a receptor complementary to ligands expressed on the pathogen. Following cytoskeletal rearrangement, further receptors engage with the pathogen in a "zipper" or "ratchet" like fashion, engulfing the pathogen into the phagosome. This figure was created with BioRender.com.

including efferocytosis, zipper phagocytosis, trigger phagocytosis, and opsonization, are discussed in more detail below.

2.1 Efferocytosis

Efferocytosis of apoptotic cells is the primary phagocytosis mechanism utilized by nonmyeloid cells. Recognition of apoptotic bodies is, therefore, critical for the clearance of apoptotic cells, and tissues have evolved ligand-receptor-based recognition as part of the initial engagement ultimately triggering efferocytosis of the apoptotic cell [7, 73, 74]. The primary component of this mechanism is the recognition of phosphatidylserine expressed in apoptotic cells [75]. During early apoptosis, phosphatidylserine molecules translocate to the cells' surface, anchoring to the membrane, where they act as an "eat-me" signal to localized phagocytes, both professional and nonprofessional [76]. Phosphatidylserine can be recognized by several receptors, including integrins $\alpha_v\beta_3$ and $\alpha_v\beta_5$ [9, 29, 34]. CD36 [29, 34], CD91 [29], and even bio-specific phosphatidylserine receptors [16, 77]. Other ligands have been proposed to induce receptor-mediated efferocytosis of apoptotic cells by neighboring nonprofessional phagocytes, including Apoptosis Inhibitor of Macrophage (AIM) recognition by Kidney Injury Molecule-1 (KIM-1) [78] and milk fat globule-epidermal growth factor 8 (MFG-E8) by integrin αvβ3 [79].

2.2 "Zipper" phagocytosis

In the initial stages of nonmyeloid cell phagocytosis, one of the primary processes is the "Zipper" mechanism [6, 80, 81]. The zipper mechanism was first coined in 1975 by Griffin *et. al* to describe the phenomena of attachment of opsonized erythrocytes and macrophages [82, 83]. Essentially, the structure is opsonized by immunoglobulins and becomes engulfed by a sequential recognition by Fcγ receptors in a "zipper" like fashion [80, 81]. Since this initial observation, similar phagocytic mechanisms have been noted that do not require opsonin-Fcγ receptor-mediated recognition, including mechanisms of phagocytosis by nonmyeloid cells. Instead, the pathogen engages with a component of the target cells' external structure. Such structures are typically cell surface integrins, adhesins, or invasins [4, 6, 34, 84]. This interaction initiates microtubule and actin rearrangements within the host cell. Following engagement, a continuous and sequential binding of the host cells "target structures" to the corresponding structures on the pathogen, leads to the complete engulfing and internalization of the pathogen by the cell in a phagosome-like vesicle, similar to that observed with opsonized mediated phagocytosis (**Figure 2,** [7, 81]).

2.3 "Trigger" phagocytosis

In contrast to zipper phagocytosis, the "trigger mechanism" is a process where engagement of the pathogen with a pathogen recognition receptor is not a critical component of the process. Some engagement with cell surface ligands may occur to secure the pathogen to the cell [80]; however, the distinguishable difference in trigger phagocytosis is that the pathogen "injects" effectors into the host cell. The injected components known as type-III (T3SS) [85] and type-IV (T4SS) [86] secretion systems result in host cell cytoskeletal rearrangements localized to the site of pathogen contact. Rearrangement generates "ruffles" along the cell surface, which then fold over the pathogen and fuse, internalizing the pathogen (**Figure 2**) [80].

2.4 Antibody opsonization

Emerging data suggest a potential role for opsonin-mediated phagocytosis in nonmyeloid cells [87–93]. Classical membrane-bound Fcγ receptors, namely FcγRI, FcγRII, and FcγRIII, and their capacity to recognize immunoglobulins are more typically associated with myeloid cell-based professional phagocytosis [57]. A more poorly understood, and somewhat atypical, class of immunoglobulin receptor, known as the neonatal Fc receptor (FcRn), is expressed ubiquitously throughout multiple tissue types, including pulmonary epithelium [92], intestinal epithelium [87], microvascular endothelium [91], and the placenta [89]. It was initially thought that FcRn is expressed in fetal and neonatal tissues; however, it has since been demonstrated that expression is sustained throughout life [90]. The FcRn has a strong affinity for albumin [90] and IgG antibodies [88]. IgG-mediated phagocytosis *via* FcRn has been noted in myeloid cells [93], but evidence for phagocytosis in nonmyeloid cells *via* this receptor is lacking. FcRn expression in nonmyeloid cells appears to be intracellular, thus lacking the capacity for extracellular surveillance [94]. Instead, it is thought that the primary function for FcRn is transcytosis of IgGs across endothelial and epithelial membranes, as opposed to opsonin-mediated phagocytosis. The fundamental machinery is, however, present in nonmyeloid tissues and models have even been proposed based on studies demonstrating IgG-mediated phagocytosis of extracellular myelin debris [7, 47].

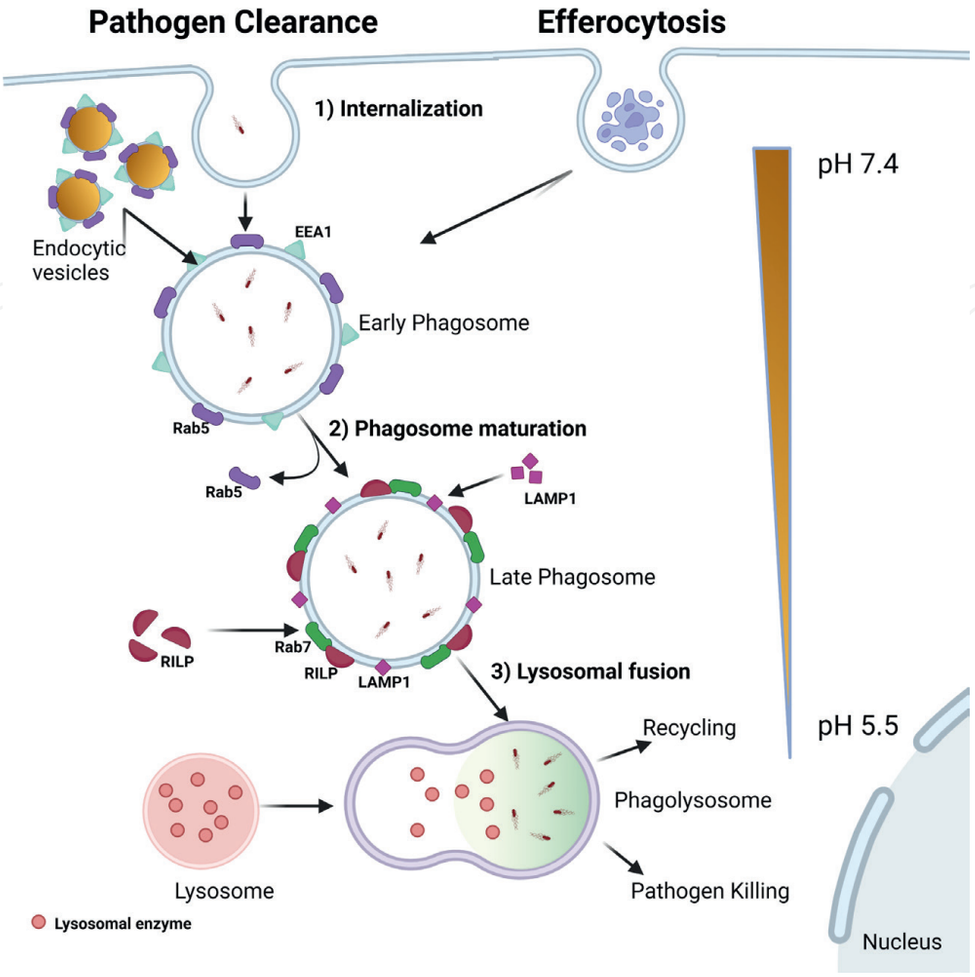

Figure 2.
Phagosome maturation. Phagosome maturation in nonmyeloid cells is like that of professional phagocytes, however less efficient. The phagocytosis process is outlined as; 1) internalization, resulting in the formation of the early phagosome, recruiting components such as Rab5 and EEA1. 2) Phagosome maturation, where Rab5 is replaced with Rab7 and factors such as RILP and LAMP 1 are recruited. 3) Lysosomal fusion, releasing factors such as degradation enzymes within the phagosome, which can result in pathogen killing and recycling of degraded products. This figure was created with BioRender.com.

3. Epithelial cell phagocytosis

The primary function of epithelial cells is to form a barrier between the internal organs and the external environment. As such these tissues have evolved to be relatively efficient in anti-pathogenic mechanisms, including the secretion of antimicrobial peptides, functional mucociliary clearance, and phagocytosis [6, 7]. The integumentary skin layer is perhaps the most obvious epithelial cell layer; however, the epithelium also lines internal organs and mucosal surface tissues, such as the respiratory tract, digestive system, genitourinary organs, and neuronal tissues, among others [95]. The physiological organization and structure of the epithelium can vary, even within the same organ system, for example, the pseudostratified epithelium that lines the proximal airways progressively changes to a simple squamous epithelium that lines the alveolar airspace [96, 97]. Despite the multiple structural phenotypes, the primary function of any epithelium is to form a barrier, a protective layer of epithelial cells connected by tight junctions [98]. Tissue-resident myeloid cells, such as macrophages, are often labeled as the first line of defense when it comes

to invading pathogens; however, it could be argued that epithelial cells provide that initial functional defense [6].

Efferocytosis appears to be a function of practically all tissues and cell types [7, 73]. Relative to professional phagocytes. The removal of damaged or dying cells can leave the barrier exposed and prone to further damage or infection. As such epithelial tissues have a remarkable capacity for repair to maintain barrier integrity and homeostasis [98]. It is well established that the primary mechanism to eliminate apoptotic epithelial cells is through extrusion into the external apical lumen [6, 99]; however, epithelial cells also engage in efferocytosis [7]. Efferocytosis is particularly important for subapical apoptotic bodies or if the epithelial lumen does not have a functional system for debris removal such as mucociliary clearance in the airways.

Apoptotic epithelia can express a wide array of "eat me" signals with the most common being phosphatidylserine [21, 29, 34]. Recognition of apoptotic cells by epithelia is somewhat less understood; however, uptake of apoptotic bodies and recognition by phosphatidylserine receptors on the epithelial cells are acknowledged to be an integral part of this process [34]. Some studies provide evidence that the process of efferocytosis observed in epithelia is distinct from that of professional phagocytes and even from other phagocytic processes [74]. Epithelial cells have a relatively strong expression of PRRs with innate capabilities of recognizing exogenous PAMPs [5, 6, 100, 101]. Activation of PRRs can induce strong inflammatory responses including cytokine release [102], however mucosal epithelial cells must maintain a bio-symbiotic relationship with natural bacterial flora and control the potential for excessive inflammatory stimulation [103]. To achieve this, many of the PRRs are either intracellular [103–106] to recognize pathogens in the process of infecting the epithelium or on the surface of a polarized epithelium restricted to the basolateral surface [101, 107] to detect pathogens that have breached the epithelial barrier. PRRs expressed on epithelial cells include the Toll-Like Receptors (TLRs), the C-type Lectin Receptors (CLRs), the NOD-like Receptors (NLRs), and the RIG-I-like receptors (RLRs) [6, 108, 109]. It has also been proposed that PRRs can also engage in zipper phagocytosis, as integral parts of internalizing pathogenic stimuli, in addition to internalization of the receptor itself to control excessive inflammatory responses [110–112]; however, it is unclear if this pathogen-induced internalization is consistent with zipper phagocytosis or even conserved in nonmyeloid cells, in principle it is a possibility. Often the overarching inflammatory response is studied in isolation from that of any possible phagocytosis response. However, it is important to recognize that there is significant overlap and control of one by the other. Indeed, it has been reported that signaling factors, such as Rac1, are necessary for phagocytosis and the subsequent control of anti-inflammatory cytokine release, key to inflammatory resolution [30]. Further insights into epithelial cell phagocytosis may well be found in the study of inflammatory cytokine biology.

A common place for epithelial phagocytosis study can be found in the retinal epithelium of the eye [113]. Separated by the blood-retina barrier [114, 115], the retinal epithelium is able to maintain a certain level of immune privilege from circulating leukocytes [116]. Whilst there is evidence for resident and infiltrating myeloid cells in these tissues [117], it is primarily the retinal epithelium that maintains homeostasis through phagocytic functions [113]. Aside from immune recognition, phagocytosis by the retinal epithelium is important for the biological process of photoreception [118]. The distal portions of photoreceptors in the eye, known as "Photoreceptor Outer Segments" (POS) are in direct contact with the retinal epithelium [119] and rich in membranous discs packaged with proteins known as opsins [120], which are

photosensitive. Exposure to light bleaches opsins to allow for signal transduction [121]. Extended exposure to these opsin-rich discs results in phototoxic damage and mature discs are shed from the distal tip to allow for the synthesis of new discs [113]. The retinal epithelium is perpetually "ensheathed" around the distal tips of photoreceptors [122], which upon shedding are phagocytosed into the retinal epithelium [119, 123]. The phagosome undergoes phagolysosomal maturation, including acidification and breakdown of the photoreceptor distal tips [113]. This entire process allows for the maintenance of long-term photoreceptors with short-lived distal tips by the retinal epithelial cells in an immune-privileged tissue. The retinal epithelium represents a prime example of a nonmyeloid cell performing specialized phagocytosis as a primary function in the homeostatic maintenance of its niche.

Internalization of pathogens by mucosal epithelium is well documented [5, 22–27]. Epithelial cells utilize both zipper and trigger mechanisms to internalize invading pathogens and engage in phagocytosis [6]. After internalization of the pathogen, the maturation of the phagosome in epithelia is akin to that of professional phagocytes [59], including markers of maturation, phagosome acidification, and lysosomal fusion [124]. The primary difference lies in the speed and efficiency when compared to professional phagocytes [125]. Despite this lack of efficiency, the contribution of phagocytosis of epithelial cells is still remarkably significant when considering cell numbers and so the impact of epithelial cell phagocytosis in pathogen clearance should not be ignored, having distinctive implications in both homeostasis and disease.

4. Endothelial cell phagocytosis

Like epithelial cells, endothelial cells also form a physical barrier, specifically in the walls of fluid systems, such as the circulatory and lymphatic systems [126]. These barriers comprise squamous endothelial cells, which form a single cell layer lining the entire system [126]. Their primary functions are to maintain the barrier and act as a filtration system for fluid-containing cells or substances into, and out of, the circulatory system [127, 128]. Significant cross talk occurs between endothelial cells and professional phagocytes as the endothelium allows leukocytes to cross through the barrier into tissues during times of infection and stress [129]. The concept of endothelial cells acting as phagocytes is not new, with some reports dating back as early as the 1920s [130]. Such a process is important for the endothelium to maintain circulatory homeostasis with effective phagocytic clearance mechanisms [129]. Phagocytosis is clearly an important function for endothelial cells to possess and execute efficiently, failure to do so can lead to serious complications such as stroke [131, 132]. Due to its importance, phagocytic clearance by endothelial cells has been termed "Angiophagy" [131, 132].

In situations of physical damage to endothelial tissue, endothelial cells can often be the first to encounter potentially pathogenic insults, particularly pathogens that enter circulation. Like epithelial cells, endothelial cells strongly express PRRs, including TLRs, NLRs, and RIG receptors [133–137]. During times of inflammation, endothelial cell PRR expression is increased [138], an important process for innate recognition of potentially invasive pathogens. It is also imperative for endothelial cells to recognize endogenous material, such as aged red blood cells, to both prevent and clear micro emboli blockages [139]. Endothelial cells express Lectin-like oxLDL receptor 1 (LOX-1), a transmembrane protein that is capable of recognizing these aged red blood cells that express phosphatidylserine [36]. Endothelial cells can also clear other cellular material, such as apoptotic cell bodies of circulating leukocytes, including that of

circulating professional phagocytes, such as neutrophils [140], and do so *via* recognition of lactadherin [141]. Endothelial cells capable of recognizing and engulfing circulating cellular material is not just a function of cellular turnover homeostasis, but this is important in reducing coagulative activity.

Angiophagy, as a phagocytic process, can be considered distinct from other mechanisms such as efferocytosis, as a specialized method of clearing vascular occlusions, which may or may not have "eat-me" recognition molecules. In several organ systems, angiophagy of large particulates, such as blood clots and fibrin, has been observed by endothelial cells in microvascular capillary structures, releasing the phagocytosed particles into the basolateral parenchyma [132, 142]. While the overall result remains consistent, angiophagy efficiency can vary between different organs [142]. The biomechanical processes of angiophagy are not well understood. Studies have demonstrated that projections of the endothelial cell wall known as "lamellipodia" extend into the occluded lumen after extensive cellular remodeling [142]. Engulfment of the occluding body occurs within a few hours, relatively quickly when compared to the entire angiophagy process, which can take several days. Post engulfment, the occluding body is trafficked to the underlying tissue where it can be further processed, often by myeloid cells [142]. A more comprehensive characterization, beyond engulfment in angiophagy, is lacking although mechanisms of phagocytosis are certainly present. Further reports have demonstrated that microparticles are internalized and retained intracellularly without any impact on barrier integrity [143].

A common endpoint of phagocytosis in some professional phagocytes is antigen presentation. After a functional inactivation of the pathogen, components of the pathogen are "presented" on the cellular surface of the phagocyte and used to activate specific lymphocytes, to initiate adaptive immune responses. This specialized function of antigen presentation is typically associated with dendritic cells but is also observed in other myeloid cells. Interestingly, antigen presentation has been observed in endothelial cells [144, 145], and even express MHCII, typically restricted to professional antigen-presenting cells, as a result of inflammatory stimulation [146]. As endothelial cells are not professional antigen-presenting cells and lack migrating capabilities important for effective antigen presentation, it is somewhat unclear as to why endothelial cells have developed antigen-presentation capabilities. It has been postulated to be important for T-cell-specific trafficking to sites of infection and stress [144]. Either way, strong phagocytosis machinery is required to process and present antigens on the cell surface.

Phagocytosis for endothelial cells is an important homeostatic process that allows luminal vasculature to remain clear of blockages and underlying tissues to remain clear of potentially pathogenic infection. The process of angiophagy to allow the extravasation of occlusions, and restoring luminal perfusion is arguably unique to endothelial cells as a process that even myeloid cells do not possess. Further work on the capabilities of endothelial cell phagocytosis could well lead to a better understanding and even treatment options for serious acute macro and microvascular disease.

5. Mesenchymal stem cell phagocytosis

Mesenchymal stem cells (MSCs) are multipotent cells capable of regeneration and differentiation into multiple cell types [147]. They reside in a wide number of tissues and give rise to cells and tissues necessary for growth, development, and tissue repair. MSCs

are frequently referred to as adult stem cells, along with hematopoietic stem cells (HSCs), which of course give rise to professional phagocytes. Adult stem cells, such as MSCs, are multipotent and distinguished from embryonic stem cells (ESCs) or laboratory-generated induced pluripotent stem cells (iPSCs), which are pluripotent with a differentiation capacity to generate cells of all three germ layers. MSCs are stromal cells, and distinct from their HSC counterparts, it is therefore perhaps surprising that an advanced cellular function such as phagocytosis has been observed. Several reports, however, have demonstrated that MSCs are indeed capable of phagocytosis. This was first reported in 2000 by Wood *et. al*, who demonstrated the ability of mesenchymal cells to clear apoptotic cells through efferocytosis in the absence of macrophages in PU.1 knock-out mice [11] and later established in 2010 when Tso *et. al* confirmed efferocytosis-like clearance of apoptotic cells by MSCs [10]. Since then, other reports have corroborated this finding in a variety of situations, confirming MSCs capabilities of efferocytosis and clearance of apoptotic cells [12, 148]. What is also surprising is the inflammatory response when apoptotic bodies are recognized by mesenchymal cells, including NF-κB signaling pathway activation [12], and MSCs can express a number of distinctive markers more closely associated with immune cells [149]. Furthermore, MSCs are capable of secreting antimicrobial peptides [150, 151] to aid in pathogen killing and clearance.

MSCs do possess a certain level of PRRs, including TLRs [152] and NOD-like receptors [153]; however, reports are lacking that definitively demonstrate exogenous pathogen phagocytosis although have suggested its plausibility [154]. Similar to endothelial cells, MSCs are capable of MHC-II type antigen presentation [155], considered to be unique to professional phagocytes, and these antigen-presenting MSCs are capable of presenting and activating T cells [156, 157]. This would suggest that phagocytosis of pathogens, to present antigens *via* MHC-II is possible; however, this has yet to be confirmed. The primary function is therefore that of a supporting role for professional phagocytes as opposed to being primary phagocytes themselves.

6. Smooth muscle cell phagocytosis

Smooth muscle is found in multiple organ systems and can provide a variety of roles, often important for the physical functions of the organ or tissue in which they reside. Unlike skeletal muscle, smooth muscle involuntarily can maintain its tone over extended periods of time [158]. The functional cellular units of smooth muscle are described as nonstriated, in that they lack the sarcomeres that their skeletal striated counterparts possess. Smooth muscle cells are rich in actin and myosin which allows for efficient contraction [159]. It would be easy to describe smooth muscle cells (SMCs) as monofunctional and homogenous; however, it would appear that they have stromal-like properties and are capable of further differentiation into multiple "macrophage-like" phenotypes capable of phagocytosis [160]. The concept of phagocytosis by SMCs was first suggested observed in 1971 by Campbell and colleagues [161], and later confirmed by Garfield *et. al* in 1975, who demonstrated uptake of yeast and latex beads by guinea pig smooth muscle [14]. Like other nonprofessional phagocytes, SMCs express the phosphatidylserine receptor and functionally recognize phosphatidylserine-rich apoptotic bodies, resulting in efferocytosis [13, 16]. Like the other nonprofessional phagocytes discussed in this chapter, SMC phagocytosis has been studied and implicated in diseases, where pathological phagocytosis is considered to play a major role, such as atherosclerosis [162, 163]. In fact, SMC phagocytosis has been a focus of investigation in atherosclerosis.

Atherosclerosis is the buildup of plaques in the subendothelial tissues of arterial macrovascular walls [164]. These plaques can obstruct blood flow through the arterial lumen, which can result in a series of vascular-related diseases. Atherosclerotic plaques comprise of "foam cells," which have phagocytosed low-density lipoproteins, which they are seemingly unable to efficiently process and resolve. Foam cells as active phagocytes are myeloid in origin, more specifically they are macrophages derived from monocytes [165] recruited into the subendothelial tissues as a result of vascular damage. However, foam cells of atherosclerotic plaques can also be derived from SMCs [49, 166], with some reports even suggesting the majority of foam cells in atherosclerotic legions to be of SMC origin [167]. Such SMCs resemble an undifferentiated precursor capable of a phenotypic switch under varying conditions [168]. The specific conditions that trigger SMCs to switch to a macrophage-like foam cell are not well known, although it appears to be KLF-4 dependent [169]. SMCs have a high abundance of LRP1, a key scavenger receptor for lipoproteins [170]. LRP1 activation will result in an influx of lipoproteins into the cell, generating a "foam cell" phenotype [171]. It is the inefficiency of SMC-derived foam cells as phagocytes that appears to be a significant factor in atherosclerosis. Despite the recognition that phagocytosis, or lack thereof, by SMCs is clearly playing a significant role in the pathophysiology of atherosclerosis, little is known about the internalization mechanism compared to the process of autophagy [172]. Studies to date have mainly focused their efforts to recreate SMC-derived foam cells and compare them to foam cells of macrophage origin in attempts to highlight key differences, instead of addressing the specific mechanisms relating to phagocytosis in SMC-derived foam cells.

7. Conclusions

Historically most investigations with regard to phagocytosis have focused on the role of myeloid cells as professional phagocytes. In this review, we have discussed nonmyeloid cell types, where roles in phagocytosis have been established. It is becoming increasingly evident that many tissue types are capable, to some extent, of phagocytosis [173]. Indeed, there are even situations of specialized phagocytic function, such as that observed in the retinal epithelia and angiophagy in vascular endothelial cells. Despite nonprofessional phagocytes being less effective when it comes to pathogen recognition, internalization, phagosome maturation, and pathogen killing, they still provide a significant contribution to phagocytosis, and, in more immune-privileged tissues, phagocytosis by nonprofessional phagocytes is imperative to maintain physiological functions.

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Conflict of interest

The authors declare no conflict of interest.

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