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MINI REVIEW

Efferocytosis: a double-edged sword in microbial immunity

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Abstract

Efferocytosis is characterized as the rapid and efficient process by which dying or dead cells are removed. This type of clearance is initiated via "find-me" signals, and then, carries on by "eat-me" and "don't-eat-me" ones. Efferocytosis has a critical role to play in tissue homeostasis and innate immunity. However, some evidence suggests it as a double-edged sword in microbial immunity. In other words, some pathogens have degraded efferocytosis by employing efferocytic mechanisms to bypass innate immune detection and promote infection, despite the function of this process for the control and clearance of pathogens. In this review, the efferocytosis mechanisms from the recognition of dying cells to phagocytic engulfment are initially presented, and then, its diverse roles in inflammation and immunity are highlighted. In this case, much focus is also laid on some bacterial, viral, and parasitic infections caused by *Mycobacterium tuberculosis* (*M. tb*), *Mycobacterium marinum* (*M. marinum*), *Listeria monocytogenes* (*L. monocytogenes*), *Chlamydia pneumoniae* (*CP*), *Klebsiella pneumoniae* (*KP*), *Influenza A virus* (*IAV*), *human immunodeficiency virus* (*HIV*), and *Leishmania*, respectively.

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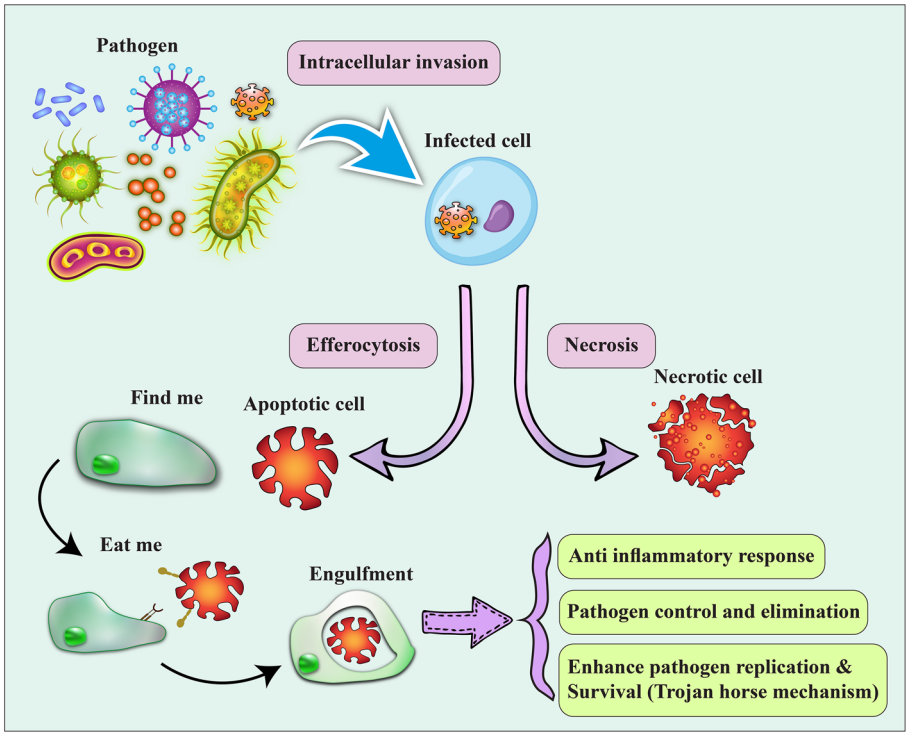
Graphical abstract



Keywords Efferocytosis · Apoptosis · Find-me · Eat-me · Pathogen clearance

Abbreviations

AC	Apoptotic cell
ATP	Adenosine triphosphate
AVC	Autoimmune valvular carditis
BAI	Brain-specific angiogenesis inhibitor
Bcl	B-cell lymphoma
CAP	Caspase
CCL	C–C motif chemokine ligand
CCR2	C–C chemokine receptor
CD47	Cluster differentiation 47
CP	Chlamydia pneumoniae
CX3CL	CX3C chemokine ligand
CX3CLR	CX3C chemokine ligand receptor
CX3CR	CX3C motif chemokine receptor
DC	Dendritic cell
EPO	Erythropoietin
EPOR	Erythropoietin receptor
ERK	Extracellular signal-regulated kinase
FasL	Fas ligand
FKN	Fractalkine
G2A	G-protein-coupled accumulation
Gas	Growth arrest-specific
HAP	Hospital-acquired pneumonia
HIV	Human immunodeficiency virus
HNP	Human neutrophil peptide
IAV	Influenza A virus
IFN-γ	Interferon gamma
IL	Interleukin
KP	Klebsiella pneumoniae
L. major	Leishmania major
L. monocytogenes	Listeria monocytogenes
LDH	Lactate dehydrogenase
LLO	Listeriolysin O
LPC	Lysophosphatidylcholine
LRP	Lipoprotein receptor-related protein
M. marinum	Mycobacterium marinum
M. tb	Mycobacterium tuberculosis
MFG	Milk fat globule-epidermal growth factor
MHC	Major histocompatibility complex
MPO	Myeloperoxidase
MR	Monnose receptor
MRSA	Methicillin-resistant Staphylococcus aureus
MTM	Myotubular myopathy
NLR	Nod-like receptor
P2Y2	Purinergic receptor

PAMP	Pathogen-associated molecular pattern
Panx	Pannexin
PCD	Programmed cell death
PE	Phosphatidylethanolamine
PGE	Prostaglandin E
PMN	Polymorphonuclear leukocyte
PPAR	Peroxisome proliferator-activated receptor
PRR	Pattern-recognition receptor
PS	Phosphatidylserine
PtdIns(3,4,5)P_3	Phosphatidylinositol (3,4,5)-trisphosphate
RA	Rheumatoid arthritis
RAB	Ras-related protein
RAC	Ras-related C3 botulinum toxin substrate
RD	Region of difference
S1P	Sphingosine-1-phosphate
S1PR	Sphingosine-1 phosphate receptor
SH	Src homology
SHPS	Src homology 2 domain-containing protein tyrosine phosphatase substrate
SIRP-α	Signal regulatory protein alpha
STAB	Stabilin
TAMs	Tyro3
TGF	Transforming growth factor
TIM	T-cell immunoglobulin mucin domain
TLR	Toll-like receptors
TNF	Tumor necrosis factor
Treg	Regulatory T-cell
UCP	Uncoupling protein
UTP	Uridine-5′-triphosphate
Vps	Vacuolar protein sorting

Introduction

As the natural process of the events leading to death inside a cell or programmed cell death (PCD), apoptosis was primarily identified by Wylie et al. in the 1970s (Kerr et al. 1972). This clever strategy regularly occurs in billions of cells in the human body every day, since it is vital for maintaining normal tissue homeostasis (Morioka et al. 2019) and regulating immunogenic responses (Grimsley and Ravichandran 2003). Apoptosis plays a role in development, as well (Wanner et al. 2021), viz. Some cells are eliminated during mammalian embryogenesis and development, and the organism manages the cell number along with the tissue size and shape (Vaux and Korsmeyer 1999). Apart from the cell death process, the removal of the cellular corpse must be accurately regulated to sustain normal homeostasis, and thus support the tissue function and integrity. The rapid clearance of apoptotic cells (ACs) is literally called efferocytosis, derived from the Latin term "efferre", which means "to take to the grave" (Yin and Heit 2021). This process is biologically characterized as the procedures of the phagocytic swallowing and digesting of the dead or dying cells (Cotter et al. 2003). This process has differences from other processes involved in cell death such as pyroptosis. Briefly, Efferocytosis is a tissue-hemostasis response via the clearance of apoptotic cells, whereas pyroptosis induces inflammation and is a form of programmed cell death that occurs in response to infection or cellular stress. The molecular mechanisms of them are different, with efferocytosis being regulated by "find-me", "eat-me", and engulfment signals, while pyroptosis involves the activation of inflammasomes and the release of pro-inflammatory cytokines. The molecular pathway of efferocytosis in pyroptosis is less well understood than the apoptosis mechanism (Purnama et al. 2023).

Efferocytosis also interacts with various biological processes such as autophagy plays an important role in inhibiting inflammation and apoptosis and by activating inflammatory cells, particularly neutrophils and macrophages promoting efferocytosis (Rochette et al. 2023).

In this case, among the most significant questions addressed are, how to distinguish between normal and dying cells, and what inhibits the random detection of normal living cells. The answer is that the dying cells from apoptosis display several morphological features, different from those observed in the cells undergoing necrotic or pathological cell death (Fink and Cookson 2005). Researchers have further demonstrated that living cells show inhibitory signals, termed "don't-eat-me", to prevent their removal. A common option for this signal in mammals is cluster differentiation 47 (CD47) located on the target cells, which is often responsible for presenting an anti-efferocytic signal toward the phagocyte through Src homology 2 (SH2) domain-containing protein tyrosine phosphatase substrate 1 (SHPS-1) (also called SIRPα) (Zhang et al. 2021). The CD47 redistribution and/or loss can be currently utilized to increase cell clearance in atherosclerosis (Anandan et al. 2021; Fernández-Ruiz 2022), cancer (Gardai et al. 2005; Kojima et al. 2016; Weiskopf et al. 2016; Werfel and Cook 2018), and autoimmune valvular carditis (AVC) (Meier et al. 2022).

However, the way such cells are known to be crucial for clearance and diagnosis is partly far from those implicated in classical immunity. In addition, these detection mechanisms are greatly redundant, complicated, and varied, with several types of cell death. In numerous PCD procedures, the cell preserves its integrity and structure, minimally long enough for its efferocytic clearance to avoid the tissues from cell disruption and exposure to toxic and immunogenic intracellular materials. The removal of apoptotic corpses accordingly

occurs by professional and non-professional phagocytes. In this respect, the former, e.g., immature dendritic cells (DCs) and macrophages, are exceedingly mobile and phagocytic, and have the ability to infiltrate a wide range of various tissues (Trzeciak et al. 2021). On the other hand, the latter have slower kinetics than their professional counterparts (Parnaik et al. 2000). The ACs engulfment can also bring certain consequences for immunity. Some studies have thus demonstrated that the mistakes in the clearance of apoptotic corpses nearly have links with inflammatory and autoimmune problems (Henson et al. 2001; Savill et al. 2002). Therefore, the ACs removal seems to inhibit the undesired immunities to self-antigens obtained from the dying cells. For instance, the AC uptakes can cause the release of the anti-inflammatory mediators, like transforming growth factor β (TGF-β), prostaglandin E2 (PGE2), and interleukin-10 (IL-10), and can further inhibit the secretion of pro-inflammatory ones, such as tumor necrosis factor-α (TNF-α) from phagocytes (Voll et al. 1997; Fadok et al. 1998b; Huynh et al. 2002). Following inappropriate efferocytosis, ACs might indeed suffer from secondary necrosis, a process resulting in the liberation of dangerous auto-antigens in the tissues and causing autoimmune disorders, e.g., rheumatoid arthritis (RA) (Thorp and Tabas 2009; Doran et al. 2020b). Efferocytosis also plays an influential role in SLE. Since unengulfed apoptotic cells in the germinal centers of the lymph nodes of some cases and the extracted macrophages from them indicate insufficient ingestion ability of apoptotic cells, the failure of dead cell clearance can be attributed to one of the reasons for SLE or in another autoimmune disease like type 1 diabetes (T1D) which pancreatic insulin-producing B cells destruct. It is believed that inefficient clearance of apoptotic pancreatic cells may promote the release of signals and auto-antigens into the media through necrosis and inflammation (Abdolmaleki et al. 2018).

Of note, AC phagocytosis is assumed as a complicated event. Overall, a mixture of pathways are used by phagocytes for the recognition of such cells (Boada-Romero et al. 2020). In this line, efferocytosis is quite regulated, and starts via ACs. Two initial events within apoptosis contain the most common, obvious superficial alterations, viz., the presence of phosphatidylserine (PS) to the exofacial leaflet of the membrane and the liberation of chemotactic cues termed "find-me" signals, by the dying cell recruiting macrophages to the cell death sites (Hoffmann et al. 2001; Korns et al. 2011). Simultaneously, macrophages can elevate the secretion of molecules and receptors, which serve as cables for catching the "me" level. Finally, the dying cell is engulfed by the macrophages, and the large efferosome at the "eat-me" step is generated (Fadok et al. 1998b; Martin et al. 2014). The importance of knowing how such pathways recognize and uptake ACs would provide a novel perspective into immunity as well as autoimmune and inflammatory conditions, along with other pathophysiological processes (Zhou et al. 2020; Gerlach et al. 2021).

Based on the recent literature, efferocytosis closely corresponds to the phagocytosis and clearance of pathogens and other foreign particles. This process has a key role to play in host defense against intracellular pathogens, including bacterial, viral, and parasitic infections caused by *Mycobacterium tuberculosis* (*M. tb*), *Mycobacterium marinum* (*M. marinum*), *Listeria monocytogenes* (*L. monocytogenes*), *Chlamydia pneumoniae* (*CP*), *Klebsiella pneumoniae* (*KP*), *Influenza A virus* (*IAV*), *human immunodeficiency virus* (*HIV*), and *Leishmania*, respectively (Chua et al. 2018; Behar and Briken 2019; Andersson et al. 2020a; Vellozo et al. 2021).

Although there have been significant advances in the understanding of efferocytosis over the past few years, some gaps have still remained in pathogen clearance and how some pathogens employ efferocytes to evade the immune systems.

This review discusses the recent advances in the knowledge of efferocytosis and microbial immunity. In the following sections, how efferocytosis identifies and takes up ACs as well as its positive and negative consequences for different pathogens are described, then some examples of pathogens that evade this defense mechanism are presented, and finally, the challenges and possibilities for future research are elucidated.

Efferocytosis

Over the past decades, more molecular techniques have been recognized for regulated cell death (Majno and Joris 1995). As well, adaptive and innate immunities have developed numerous ways to prevent the detection of normal body cells, and concentrate on foreign structures to kill and/or remove them to conserve the tissue integrity and hemostasis. For instance, dying cells display molecular signs as signals to phagocytes, and regulate phagocytic and immune responses (Tajbakhsh et al. 2022a). These signals are not only the molecules implicated in apoptosis, but also signal pathways moderating the uptake processes. The initial step for knowing about cell clearance is to demonstrate the efferocytosis mechanism (Peter et al. 2008). In addition, a dying cell uptake for the efferocytosis process has been particularly suggested to promote the uptake ability of others, presenting ways for subsequent engulfment (Nakaya et al. 2008). Generally, efferocytosis is a process that involves four steps, viz., phagocyte attraction, recognition, engulfment, and post-engulfment responses (Gheibi Hayat et al. 2019) (Fig. 1).

There is a long way to explain the special pathways directing professional and non-professional phagocytes to dying cells prior to losing the membrane integrity. Some studies have accordingly reported that ACs liberate chemotactic

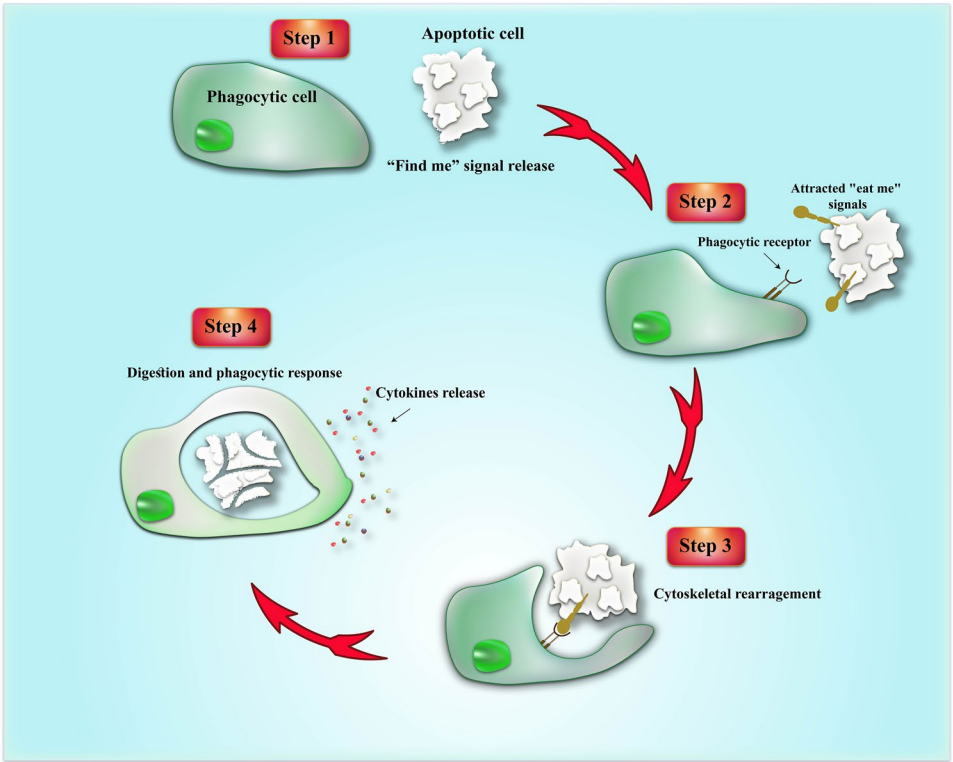


Fig. 1 Efferocytosis steps: "find-me", "eat-me", and "post-engulfment" signaling. Step 1: Dying cells release "find-me" signals to recruit phagocytes to cell death sites. Step 2: Phagocytes sense "find-me" signals via special receptors. Step 3: Intracellular signaling induced within the ligand–receptor interactions leads to cytoskeletal rearrangements, and dying cells are exposed to a variety of signals on their surfaces, interacting with receptors on the phagocytic membrane through "eat-me" signals. Step 4: Proper digestion occurs following the uptake of dying cells by phagocytes. In combination, these signals regulate the efferocytosis

signals to attract monocytes dependent on a caspase-3 (CAP-3) (Nagaosa et al. 2003). Another hypothesis is that the alterations in the composition of membranes caused by apoptosis may release electric signals, capable of attracting phagocytes (Zhao et al. 2006). To promote their engulfment, ACs display specific signals, like "find-me" and "eat-me". However, there is a critical issue about distinguishing ACs from non-ACs (Birkle and Brown 2021). The latter produce the signals of "don't-eat-me", blocking their clearance (Gardai et al. 2006; Kelley and Ravichandran 2021). In the following sections, all the mentioned signals are briefly discussed.

"Find-Me" signals

The first step in efferocytosis is to recognize targeted ACs through phagocytes via the "find-me" signals, released by the dying cells (Tajbakhsh et al. 2022b). In other words, chemokines discharged from ACs cause phagocytes to direct to cell death sites. Some "find-me" signals include lysophosphatidylcholine (LPC) that recruits macrophages via reaction with the G-protein-coupled (G2) accumulation (G2A) receptor; CX3C chemokine ligand 1 (CX3CL1), released from apoptotic human B cells in extracellular vesicles; sphingosine-1-phosphate (S1P), produced by ACs and driving the secretion of erythropoietin (EPO) in macrophages as well as extracellular signal-regulated kinase (ERK) and peroxisome proliferator-activated receptor (PPAR) pathways, activated by the EPO-erythropoietin receptor (EPOR) axis; as well as nucleotides like adenosine triphosphate (ATP) and uridine-5′-triphosphate (UTP) that are activated and released in the environment by the pannexin-1 (Panx1) channel (Ravichandran 2011). Generally, ACs liberate the "find me" signals, including S1P, LPC, nucleotides, and fractalkine (FKN, i.e., CXC3CL1). Such molecules are capable of attaching to their related receptors (e.g., G2A, CX3C motif chemokine receptor 1 [CX3CR1], purinergic receptor [P2Y2], and S1P-R1/5, respectively) found on the surface of phagocytes (Fig. 2).

"Eat-Me" signals

Following the migration and recognition of phagocytes, the engulfment of ACs occurs via a collection of molecular episodes, named the "eat me" signals (Banerjee et al. 2021). Such signals are unique surface markers on ACs that connect to their receptors on the phagocyte surface. In the following, they initiate signal cascades in the cell, reorganize the cytoskeleton, and result in engulfment (Hanayama et al. 2002; Li 2012). Numerous "eat me" signals have been yet identified, like calreticulin, which mediates recognition and engulfment via low-density lipoprotein receptor-related protein 1 (LRP1) receptors. In addition, the most commonly studied "eat-me" signal is PS, frequently migrating to the outer leaflet during apoptosis (Naeini et al. 2020), although PS in viable cells is maintained on the inner leaflet of lipid bilayer through ATP-dependent translocases (Balasubramanian and Schroit 2003).

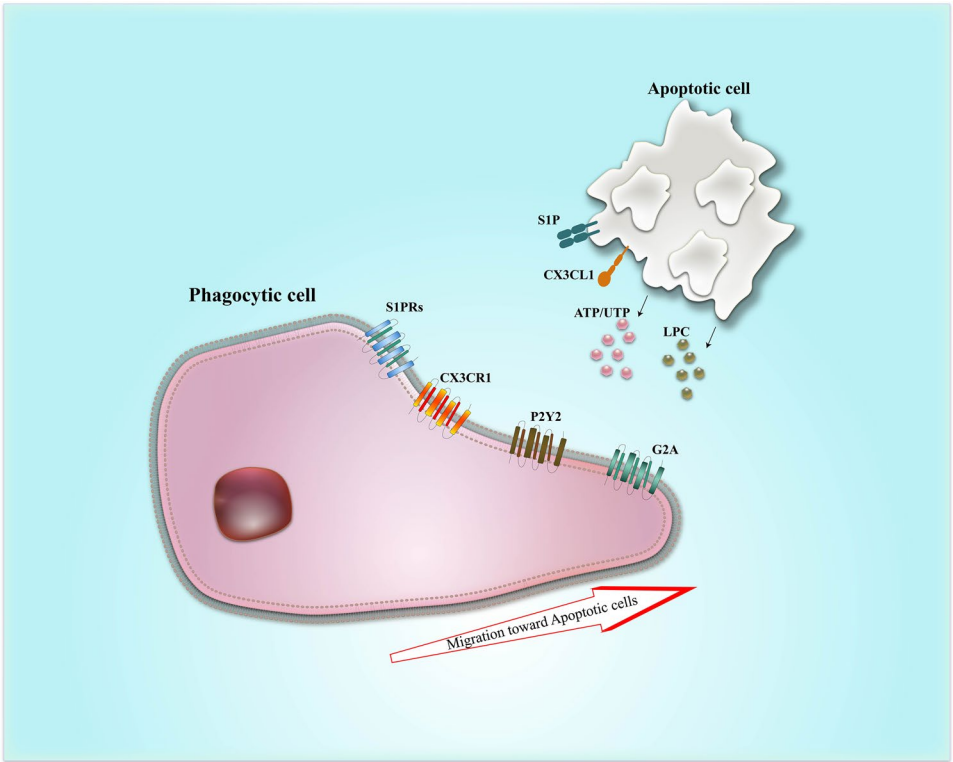


Fig. 2 "Find-me" signal. Chemotactic factors induce macrophages to identify and migrate toward ACs. Low levels of nucleotides, ATP and UTP, FKN also known as CX3CL1, LPC, and S1P released by ACs attract motile phagocytes to the proximity of the cell, undergoing apoptosis. Phagocytes then sense these "find-me" signals via receptors viz. P2Y2, CX3CLR, G2A, and S1PRs. ATP, adenosine triphosphate; UTP, uridine-5'-triphosphate; CX3C, chemokine ligand 1; LPC, lysophosphatidylcholine; S1P, sphingosine-1-phosphate, P2Y2, Purinergic receptor; CX3CLR, CX3C chemokine receptor 1; G2A, G-protein-coupled receptor; S1PRs, Sphingosine-1 phosphate receptors

Phagocytes also directly attach to PS on ACs via different receptors, such as the family of T-cell immunoglobulin mucin (TIM), including TIM-3, TIM-1, and TIM-4 (Miyanishi et al. 2007; Pham et al. 2008; Kim et al. 2020), stabilin-2 (STAB2), and brain-specific angiogenesis inhibitor 1 (BAI-1) (Park et al. 2007; Hochreiter-Hufford and Ravichandran 2013) or indirectly to the target cell by bridging molecules or essential relevant receptors, like milk fat globule-epidermal growth factor-8 (MFG-E8) that can link PS and indirect PS receptors, αvβ3/αvβ5 integrins (Hanayama et al.; Kelley and Ravichandran 2021), growth arrest-specific 6 (Gas6)/tyro-3 (TAM) receptors, etc. (Hochreiter-Hufford and Ravichandran 2013).

Furthermore, it is not yet kwon whether PS detection alone is enough to initiate phagocytosis. Some investigations have accordingly revealed the adequacy of PS detection to remove ACs (Fadok et al. 1998a); however, some others have suggested the opposite. In this regard, exposure to PS occurs on living cells, which are not engulfed. There are also multiple documents regarding oxidized PS on AC surface (Kagan et al. 2002), and thus, the PS modification is a way to identify dead cells (Gheibi Hayat et al. 2019) (Fig. 3).

"Digest-Me" signals

Finally, after engulfment, the post-engulfment processing of ACs, there is a "digest-me" step, which includes phagosome maturation, and then, the fusion of mature phagosome with lysosome. The existence of hydrolytic enzymes also allows the engulfed cargo recycling and degradation (Hochreiter-Hufford and Ravichandran 2013; Fountain et al. 2021).

On the one hand, there is not very much information about the routes of phagosome maturation prior to being fused with lysosome, but some recent studies have found this process being influenced by aging and neurodegeneration, wherein the degradative capacity of lysosome is declined with age (De Maeyer and Chambers 2021). Other studies have further demonstrated that the first step of phagosome maturation occurs by recruiting dynamin to the interface of AC and phagocyte. Dynamin results in Ras-related protein (RAB5) recruitment and activation (Fountain et al. 2021), and the activated RAB5 accordingly increases vacuolar protein sorting 34 (Vps34) activation, generating phosphatidylinositol (3,4,5)-trisphosphate ($PtdIns(3,4,5)P_3$) on the phagosome surface, and then cleared by myotubular myopathy 1 (MTM-1). MON1 homolog A (MON1a) and CCZ1 homolog (CCZ1) (as its binding partners) also tie RAB5, triggered and recruited by RAB7, to the phagosome. During this step, the phagosome fusion with the lysosome occurs by the homotypic fusion and vacuole protein sorting (HOPS) complex recruitment and RAB7 activation (Kinchen and Ravichandran 2008; Lam and Heit 2021; Taefehshokr et al. 2021), and then, acidic nucleases and proteases get activated, thereby degrading AC targets (Lennon-Duménil et al. 2002; Nguyen and Yates 2021). Phagocytes usually work on multiple bodies at the same time; hence, they effectively progress

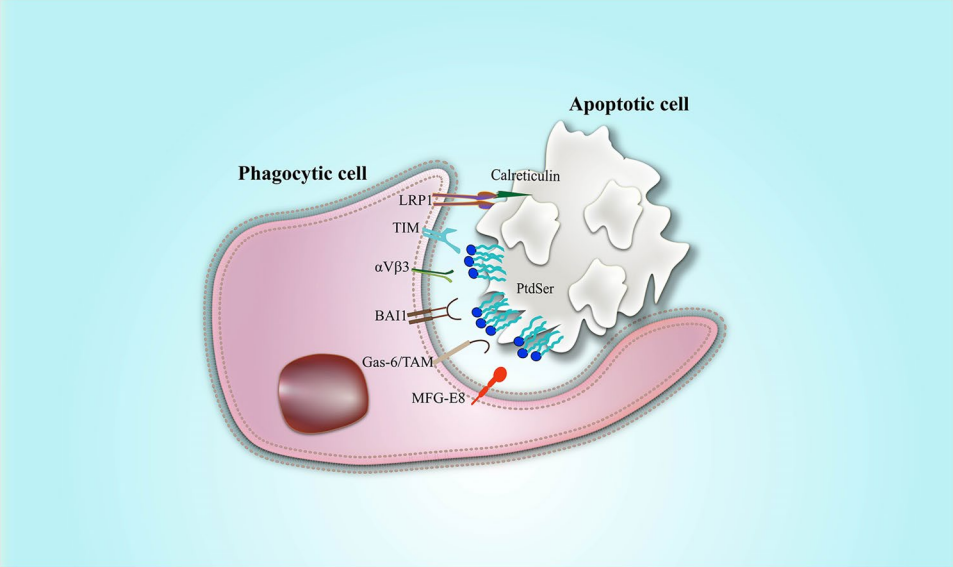


Fig. 3 A schematic overview of molecular associations that drive the "eat me" step. The engulfment of ACs is primarily driven by the recognition of PS, which is the most common "eat me" signal, on AC, either directly by receptors such as BAI-1 or via bridging molecules, such as MFG-E8, which engages other surface engulfment receptors, αvβ3 and Gas6. Other "eat me" signals, calreticulin, mediate engulfment via the receptors, LRP1. PS, Phosphatidylserine; BAI-1, Brain-specific angiogenesis inhibitor 1; MFG-E8, Milk fat globule-EGF factor 8; LRP1, Low-density lipoprotein receptor-related protein 1

AC clearance, and keep homeostasis (Hochreiter-Hufford and Ravichandran 2013).

Furthermore, some studies have shown that the mitochondrial membrane protein, uncoupling protein 2 (UCP2), has positively regulated the engulfment capacity of phagocytes (Kourtzelis et al. 2020). The UCP2 overexpression accordingly elevates AC phagocytosis under in vitro conditions, and diminishes the secretion of UCP2-reduced phagocytosis under both in vivo and in vitro conditions (Park et al. 2011; Tajbakhsh et al. 2019) (Fig. 4).

Efferocytosis and pathogen clearance

Efferocytosis interacts with various types of immune system cells for proper functioning. Some examples in this field include dendritic cells efficiently mediating efferocytosis to suppress the immune response to self-antigens. Efferocytosis has also been shown to promote the resolution of inflammation and shift macrophages toward a pro-resolving M2 phenotype. Neutrophils can be inactivated via apoptosis, forming apoptotic cells that are engulfed by macrophages, promoting efferocytosis. Other Immune Cells like Regulatory T cells (Tregs) have also been found to interact with the efferocytosis process, to modulate macrophage efferocytosis in animal models of inflammatory conditions, including atherosclerosis, and acute lung injury (ALI) or Ly6C + monocytes were reported to induce efferocytosis via TLR ligation are another example of interaction between immune cells and efferocytosis process (Ge et al. 2022a).

Another aspect of programming is to know about efferocytosis, resulting in host immune defense and macrophage programming (Arnold et al. 2007). Different pathogens employ various virulence factors for targeting and modifying the physiological procedures of host to maintain stability within them (Baxt et al. 2013), in contrast to the host cells that possess diverse tools to manage infection, including apoptosis. The activation of apoptosis by the CAP-8-dependent (extrinsic) and CAP-9-dependent (intrinsic) pathways or the induction of apoptosis in infected cells through cytotoxic T lymphocytes by the exocytosis of cytotoxic granules, containing granzymes and perforin, or Fas/Fas ligand (FasL) pathway, eventually causes the infected cell death (Dockrell et al. 2001; Barry and Bleackley 2002; Ashida et al. 2011).

As the infected cells undergo apoptosis, two possibilities can be described for the fate of microbes inhabiting in them:

A. Host antimicrobial activity: The elimination of pathogen can occur alongside the AC engulfment.
B. "Trojan Horse" model: The pathogen applies efferocytosis to separate into novel cellular hosts.

New findings have accordingly demonstrated one of the features of efferocytosis as its role in host defense (Mytych et al. 2021). The reparative/anti-inflammatory mediators induced by efferocytosis can also serve in a paracrine or an autocrine manner on local macrophages and monocytes, and tissue cells (Mao 2021).

In this process, macrophages are able to detect intracellular pathogenic agents inside ACs with infection, although the mechanisms of this process have remained inadequately described. It seems that the Toll-like receptor (TLR) engagement is needed in the maturing efferosome (Korns et al. 2011).

The DCs are also effective in host defense, so that they can activate some effector T cells, engulfing ACs infected with bacteria (Penteado et al. 2017). Moreover, pathogen-associated molecular patterns (PAMPs) located on infected

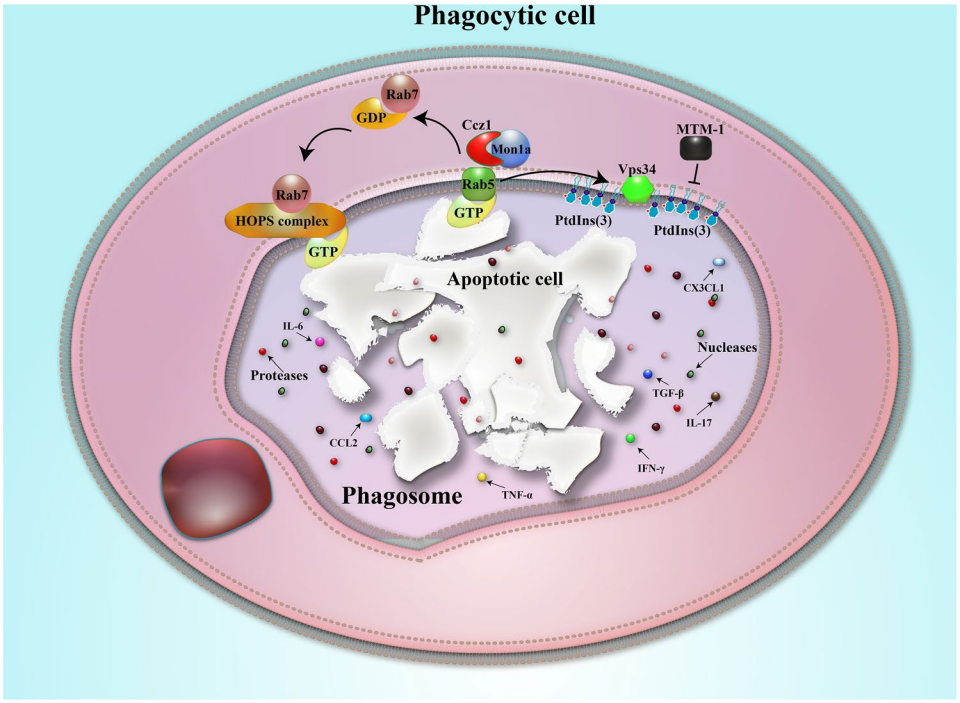


Fig. 4 The phagocyte processes the engulfed corpse and makes proper digestion through various steps. Macrophages digest and degrade AC debris, activating numerous metabolic signaling pathways. Engulfment is then initiated through the binding of "eat-me" signals to receptors on the phagocyte membrane, and subsequent actin-mediated membrane rearrangement to surround the dead cell. The maturation of the phagosome occurs via the activity of Vps34, PI3P, and RAB proteins. Early phagosome transition to late phagosome, including the small GTPase RAB7, and the concomitant loss of early markers, such as RAB5. In addition, the HOPS complex interacts and activates RAB7 to allow the fuse of the phagosome with the lysosomal network. Vps34 and PI3P are also needed for the optimal progression of phagosome maturation. Vps34, vacuolar protein sorting 34; PI3P, phosphatidylinositol-3-phosphate; RAB, Ras-associated binding; HOPS, homotypic fusion and vacuole protein sorting

ACs trigger the IL-6 production and TGF-β expression, facilitate the CD4 + T-cell differentiation to T helper cells (TH17 cells) generating IL-17, and then block the regulatory T-cell (Treg cell) secretion (Torchinsky et al. 2009; Krakauer 2019).

To come to the point, if efferocytosis happens rapidly, different fates can be observed for the immune response and the pathogen, based on the pathogenic agents and the dying cell types in which it is located, the efferocyte type, and other factors, like genetic polymorphisms (Kim et al. 2019). On the opposite side, if phagocytes do not rapidly engulf the dead cells infected, living pathogens are distributed due to pathogen-mediated pore generation or leakage of plasma membrane, as events occur in the secondary necroptosis or cell necrosis. Living pathogens can be further dispersed to the site as a result of pathogen-induced pore formation or plasma membrane leakage, once events arise in the secondary cell necrosis or necroptosis (Blander et al. 2012; Martin et al. 2014).

Following efferocytosis, most pathogens are also destroyed by macrophage. Nevertheless, some human pathogens have adapted and bypassed this defense mechanism and hijacked it to alternatively survive and spread via a “Trojan horse” mechanism. In other words, some pathogens may invade the phagocyte via efferocytosis and accelerate their multiplication and spread by representing the CD47 on the surface of infected cells, which prevents the cells from being efferocytosed (Brown and Neher 2012). For instance, some bacteria species, like methicillin-resistant *Staphylococcus aureus* (MRSA) via the "don't-eat-me" signal, CD47, on the affected cells can evade uptake and elimination (Greenlee-Wacker et al. 2014). Although there have been only a few investigations on the effect of apoptotic cell removal on viral infections. It was reported that infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) could perform widespread cell apoptosis and also increase the release of chemokines and cytokines to create a cytokine storm and impair macrophage function and hinder the removal of apoptotic cells (dos-Santos et al. 2021; Dutta et al. 2022).

A few examples of different pathogens are provided in the next sections (Table 1).

Table 1 A summary of the interaction between some pathogens and Efferocytosis

Pathogens	Effect of Efferocytosis	Pathogen fate	References
Bacterial Infection			
Mycobacterium tuberculosis	Efferocytosis has a central function in the elimination of M. tb	Elimination of M. tb	(Tan et al. 2006; Winau et al. 2006; Martin et al. 2012)
	M. tb restrains the apoptosis of host cells and efferocytosis by regulating anti-apoptotic (Mcl-1, A1) and pro-apoptotic (Fas, TNF receptor 2 [TNFR2]) proteins	Survival of M. tb	
Mycobacterium marinum	employ the efferocytic routes	escape from killing	(Demarco et al. 2020), (Muse Davis and Ramakrishnan 2009)
	use "Trojan Horse" mechanisms	assist their distribution	
Listeria monocytogenes	employing Efferocytosis; this bacteria use the pore-forming toxin listeriolysin O (LLO) and phospholipase C enzymes to evade the phagosome in host cells and cell-to-cell spreading	evade innate immunity and spread throughout the host	(Quereda et al. 2021))Sommer 2020)
Chlamydia pneumoniae	employing Efferocytosis and suppression of inflammation and immune response via the “forget me” signal	evading the immune response and spreading	(Rupp et al. 2009; Thiriot et al. 2020)
Klebsiella pneumoniae	Different mechanisms employed by K. pneumoniae strains to modulate cell death and immune responses	bacterial removal	(Jorgensen et al. 2016), (Demarco et al. 2020), (Codo et al. 2018; Lin et al. 2020)
	The liberation of intracellular soluble residues, with other elements can cause cell recruitment toward the region of infection, triggering the efferocytosis of pyroptotic-infected cells and also pyroptotic cells display the "eat-me" and "find-me" signals, enabling the second phagocytes to migrate and identify the dying cells. On the other hand, some strain of K. pneumoniae is able to inhibit inflammasome activation and pyroptotic cell death by inducing IL-10 production	allowing bacterial survival in the host	
Viral infection			
Influenza A virus (IAV),	Efferocytosis interferes in virus spreading, The recognition of cells by neutrophils and macrophages also arises via identifying exposed PS on the dying cell surface, when the cells undergo apoptosis	virus spreading	(Lim et al. 2020)
SARS-CoV-2	uptake of dying cells infected with SARS-CoV-2 by macrophages can switch the effector response to Efferocytosis from an anti-inflammatory function to a pro-inflammatory one	inefficient clearance of dead cells and potential tissue damage	(Salina et al.2022)

Table 1 (continued)

Pathogens	Effect of Efferocytosis	Pathogen fate	References
Human immunodeficiency virus (HIV)	PS displayed on the cells infected with HIV-1 causes the phagocytic elimination of affected cells	inhibits virus spread	(Chua et al. 2019a)
Parasitic infection			
Leishmania	Efferocytosis of dying neutrophils may lead to harmful or beneficial after-effects for the parasite	Elimination of pathogen Inhibiting the efficient elimination of parasites and pathogens employ efferocytosis to penetrate into a host cell	(Peters et al. 2008; Carreira and da Silva 2021)

Bacterial infection

M. tb

Efferocytosis has a central function in the elimination of *M. tb*. The bacterium is transmitted by inhaling droplets liberated from an infected person's lungs, usually by sneezing or coughing. It has been estimated that 40–70% of infected people kill *M. tb* via the innate immunity without T-cell support (Rosenthal 1965; Dannenberg Jr and Rook 1994). Tissue DCs and alveolar macrophages also participate in immune defense, and infected host cells generate inflammatory cytokines, which drive the migration and recruitment of DCs and lymphocytes to lymph nodes, wherein cellular immunity begins (Cooper 2009).

Lately, emerging evidence has demonstrated that macrophages use not only the route of phagosomes to kill *M. tb,* but also additional antimicrobial effector functions, like efferocytosis, to cooperate in the restriction of mycobacterial proliferation (Ge et al. 2022b).

The connection between efferocytosis, macrophages, and mycobacteria, was represented by Fratazzi et al. (Fratazzi et al. 1997). Some studies have further mentioned that unaffected macrophages decreased *M. tb* growth in apoptotic macrophages through efferocytosis (Martin et al. 2012). Infection with the virulent *M. tb* also leads to apoptosis (Kumar et al. 2020). The macrophages infected with *M. tb* are swallowed by unaffected bystander macrophages, and subsequently the apoptotic materials are directed toward the lysosome site. In addition, human neutrophil peptide-1 (HNP-1), as an antimicrobial peptide secreted by neutrophils, is directed into infected macrophages via efferocytosis and kills intracellular *M. tbs*. The cross-presentation of antigens, originated from efferocytosed apoptotic blebs via macrophages, is another defense mechanism of efferocytosis against *M tb.* Such antigen-bearing vesicles can also alert protective CD8 + T cells (Tan et al. 2006; Winau et al. 2006; Martin et al. 2012).

The other side of the coin is that *M. tb* restrains the apoptosis of host cells and efferocytosis by regulating anti-apoptotic (Mcl-1, A1) and pro-apoptotic (Fas, TNF receptor 2 [TNFR2]) proteins (Keane et al. 2000). *M. tb* can further trigger the upregulation of anti-apoptotic genes of anti-apoptotic B-cell lymphoma 2 (Bcl-2) family, like A1 and Mcl-1 (Kremer et al. 1997; Sly et al. 2003). Moreover, *M. tb* suppression of extrinsic apoptosis through macrophage infection downregulates death receptors, like Fas (CD95) and the soluble TNFR2 (sTNFR2) (Krakauer 2019; Borkute et al. 2021). The sTNFR2 then binds to TNF in the extracellular environment, and inhibits its binding to the TNFR1 (Oddo et al. 1998; Behar and Briken 2019).

The cell death variant can thus exert a direct impact on the outcome for pathogenic agent. Multiple virulent *M. tb*

species have been accordingly adapted to redirect apoptosis toward a programmed necrotic pathway, which allows the release of bacteria from the disrupted cell, promoting pathogen distribution (Molloy; Duan et al. 2002; Behar et al. 2011; Amaral et al. 2014).

Moreover, the role of the "eat-me" signals implicated in the efferocytic mycobacterial uptake of infected cell needs to be clarified. Some studies have represented the knockout of human macrophage cell surface, the monnose receptor (MR), applying anti-MR antibody or pre-incubation via competitive soluble sugars (mannan [polysaccharide] and N-acetylglucosamine [GlcNAc]) (Garcia-Aguilar et al. 2016), or suppressing TIM-4 (Martin et al. 2012; Liu et al. 2020) declining the uptake of apoptotic *M. tb*-infected macrophages with the aid of unaffected ones.

M. marinum

M. marinum can employ the efferocytic routes to escape from killing or even use "Trojan Horse" mechanisms to assist their distribution. Following the *M. marinum* uptake via zebrafish macrophages, the infected macrophage experiences apoptosis, and is engulfed by other non-infected macrophages (Demarco et al. 2020). These events lead to the infection spreading through efferocytosis for elevating granuloma burden and seeding secondary granulomas via region of difference 1 (RD1) virulence factor (Muse Davis and Ramakrishnan 2009).

L. monocytogenes

Some pathogens are able to exploit efferocytosis to evade innate immunity and spread throughout the host L. monocytogenes is one of them. The dissemination of *L. monocytogenes* is enhanced in a host employing efferocytosis (Quereda et al. 2021). These bacteria use the pore-forming toxin listeriolysin O (LLO) and phospholipase C enzymes to evade the phagosome in host cells and cell-to-cell spreading (Mostowy and Cossart 2012; Sia and Rengarajan 2019). LLO encourages the liberation of bacteria-carrying bulges from the host cell via the formation of membrane-originated vesicles with exofacial PS. The PS-binding receptor, TIM-4, also has a function in the effective intercellular spread by *L. monocytogenes* in macrophages (Czuczman et al. 2014b; Sommer 2020). In more detail, following lysis of the phagocytic elements in host cells, the L. monocytogenes surface protein ActA can polymerize actin in the cytosol, which allows the formation of bacteria-containing membrane vesicle, the structures that are later internalized by neighboring cells to result in cell-to-cell spreading of L. monocytogenes (Lambrechts et al. 2008). In both phagocytic and non-phagocytic cells, ActA-mediated actin-based motility was proposed to allow close apposition of bacteria to the cell membrane, where secreted LLO may damage the cell membrane and induce externalization of phosphatidylserine (PS), a hallmark of apoptotic cells at cell membrane that accelerates efferocytosis. The PS-positive vesicle structures containing L. monocytogenes are later recognized by the PS-binding receptor TIM-4 on macrophages to encourage phagocytic uptake and cell–cell spreading (Czuczman et al. 2014a; Tsai and Chen 2020). Interestingly, efferocytosis also induces the secretion of vascular endothelial growth factor (VEGF) suggesting that in patients with listeria meningitis, the bacteria spread through blood vessels, cerebrospinal fluid, and immune cells into the brain (Engelen-Lee et al. 2018).

Chlamydia pneumoniae (CP)

Chlamydia pneumoniae is a common pathogen in acute infections of the respiratory tract like pneumonia and is associated with chronic lung sequelae (Rupp et al. 2009).

CP infects and so hides in the neutrophil granulocytes until these cells become apoptotic, and consequently absorbed by macrophages. Actually, neutrophils, acting as a transport vehicle, to the macrophages. The macrophages infected with *CP* show an increased replicative activity of chlamydiae as compared with the direct infection of macrophages. Moreover, the transfer of apoptotic polymorphonuclear (PMN) leukocyte infected with *CP* to macrophages enhances the production of TGF-ß, but the direct engagement of macrophages with chlamydiae is identified via rising TNF-α response. In other words, chlamydia pneumoniae suppression of inflammation and immune response via the “forget me” signal is characterized by the release of anti-inflammatory cytokine TGF-ß and down-regulation of the pro-inflammatory cytokine TNF-α (Rupp et al. 2009). Another aspect is the role of the annexin-V in the inhibition of efferocytosis and reduced spread of chlamydial infection to macrophages (Rupp et al. 2009; Thiriot et al. 2020). With these specifications, efferocytosis has been investigated as a mechanism for evading the immune response by Chlamydia pneumoniae.

Klebsiella pneumoniae (KP)

The Gram-negative *KP* is responsible for severe bacterial hospital-acquired pneumonia (HAP) (Broberg et al. 2014). During its pathogenesis, monocytes and neutrophils are recruited toward the infection site for their performance, and are influenced by cell death variants. The pyroptosis also occurs following the infection of this bacterium through the activation of inflammasome. These bacteria are capable of escaping toward the cytosol from the phagolysosome (Demarco et al. 2020). At that place, they interact with pattern recognition receptors (PRRs), in particular with

nod-like receptors (NLRs), responsible for the recognition of bacterial residues in the host cytosol, like peptidoglycans (Martinon et al. 2004) and endogenous alarm signals (Martinon et al. 2002; Shi et al. 2003; Zheng et al. 2021a). These receptors can activate inflammasome. The formation of inflammasome via bacterial products and CAP-11 also activates CAP-1. Consequently, the pro-IL-1β is cleaved into IL-1β. The liberation of intracellular soluble residues, like lactate dehydrogenase (LDH), IL-1β with other elements can cause cell recruitment toward the region of infection, triggering the efferocytosis of pyroptotic-infected cells, and consequently bacterial removal. Furthermore, pyroptotic cells display the "eat-me" and "find-me" signals, enabling the second phagocytes to migrate and identify the dying cells in the same way as apoptotic bodies (Jorgensen et al. 2016).

Nevertheless, some studies have reported the role of this bacterial capsule in the synthesis of IL-10 at the infection site, and the role of elevated IL-10 concentration to decrease the expression of pro-inflammatory cytokines (Yoshida et al. 2001). Recent research has further presented the mechanism of action for the clinical strains of this bacterium based on IL-10 by blocking CAP-11 and -1. Indeed, IL-10 impedes the inflammasome, thus disrupting the formation of inflammasome and inducing cell death by pyroptosis and the infected cell efferocytosis. This inhibition helps this pathogenic strain to escape elimination, and allows bacteria to spread (Codo et al. 2018; Lin et al. 2020).

Viral infection

Although no adequate work is available on the performance of efferocytosis to prevent viral replication, a few viruses can be mentioned.

IAV

IAV is the seasonal and pandemic morbidity and mortality, which is still a serious health problem and a life-threatening agent around the world. In this case, several mechanisms are involved in body homeostasis, such as mucociliary clearance and phagocytosis, so various approaches must be developed to effectively control influenza, which in turn, needs to enhance the knowledge about them and the fundamental scientific and effective pathways of host cell reactions versus this condition (Paget and Trottein 2019). Following being infected with *IAV*, the clearance of the infected cells occurs by innate and adaptive immune responses, particularly mediated by cytotoxic CD8 + T cells (Chan et al. 2021). The recognition of cells by neutrophils and macrophages also arises via identifying exposed PS on the dying cell surface, which starts presenting PS, which is normally in the inner leaf of cell membrane, but displayed on the outer layer when the cells undergo apoptosis (Lim et al. 2020); in this way, efferocytosis interferes in virus spreading (Shiratsuchi et al. 2000; Hashimoto et al. 2007; Mukherjee et al. 2017; Lim et al. 2020).

SARS-CoV-2

Recent research suggests that the uptake of dying cells infected with SARS-CoV-2 by macrophages can switch the effector response to efferocytosis from an anti-inflammatory function to a pro-inflammatory one. This exacerbates the secretion of inflammatory cytokines, such as IL-6 and IL-1β, contributing to the cytokine storm observed in severe COVID-19 cases. Additionally, this shift in macrophage function impairs their ability to continually clear apoptotic cells, leading to inefficient clearance of dead cells and potential tissue damage. Histological assessments and analysis of scRNAseq datasets suggest that the efferocytic capacity of lung macrophages is impaired in COVID-19 patients, potentially contributing to respiratory complications and susceptibility to secondary bacterial infections (Salina et al. 2022).

HIV

HIV, dengue, and Ebola enveloped viruses use apoptotic (PS) mimicry for penetration into host cells. As mentioned in the previous section, PS on the surface of dead cells acts as "eat-me" signals for phagocytes to remove the dead cells, using phagocytosis, and inhibit autoimmune and inflammatory reactions (Chua et al. 2019a). Recent studies have shown that *HIV*-1 triggers the secretion of PS on the target and infected cells, and exposes PS on its envelope, capable of providing or preventing multiple stages of the replication of *HIV*-1. The virus triggers PS on target cells at the step of viral attachment (Dupont and Sattentau 2020). The envelope proteins of *HIV*-1 also attach to CD4 (its receptor) and C–X–C chemokine receptor type 4 (CXCR4) or C–C chemokine receptor type 5 (CCR5) (co-receptors), and issue signals, capable of triggering the exposure of PS on target cells through the activation of transmembrane protein 16F (TMEM16F) as a phospholipid scramblase (Masters et al. 2013; Chua et al. 2019b).

In addition, molecular pathways of viral binding are related to the envelope PS. In this process, protein S and Gas6 direct viral binding to target cells by bridging envelope PS to TAM receptor tyrosine kinase on the target sites of the cells (Ranta and Kumar 2020). The penetration of the enveloped virus and target cells by attaching to envelope PS and integrins αVβ3 and/or αVβ5 on target cells also occur via MFG-E8. Type 1 membrane proteins (TIM-1, CD300a, TIM-4, and TIM-3) directly bind envelope PS. Axl/Gas6 and TIM-1 and -4 also enable the infection of enveloped virus more effective than other PS-binding molecules. Moreover, CD300a and TIM-1 are able to provide the attachment of

the virus through binding to phosphatidylethanolamine (PE) exposed on the envelope. On the opposite side, the molecular pathway of phagocytic removal of cells infected with *HIV*-1 via macrophages ensues by the induced PS located on CD4 + T cells (Chua et al. 2019a). At a late apoptotic step, the infected cells produce great PS concentrations and low amounts of viral proteins. In addition, the cells generate high levels of viral proteins and low levels of PS. Moreover, at this step, protein S leads to phagocytic clearance of the cells infected with *HIV*-1 through bridging PS on the infected cells to the Mer on macrophages (Li et al. 2014; Bracq et al. 2018; Chua et al. 2019b).

Briefly, PS displayed on the cells infected with *HIV*-1 causes the phagocytic elimination of affected cells, displayed on target cells, simplifies the fusion process of *HIV*-1, and PS displayed on HIV-1 envelope then provides the attachment of virus while interfering with a viral liberation by the interplay with the PS-binding molecules (Chua et al. 2019b).

Since such performances can provide or prevent the replication of virus at various steps of viral life cycles, further work is needed to determine how *HIV*-1 interplays significantly with such molecules to monitor the exposure levels of PS on cells and viral envelopes, and affect efferocytosis.

Parasitic infection

The parasitic species of *Leishmania* develop a variety of human diseases, with the formation of granulomatous lesions in the skin or other organs like spleen and liver, thereby affecting human health all over the world, especially among the poor people. T-cell cytokines, IL-4 and interferon gamma (IFN-γ), have a key performance in adaptive immune system versus *Leishmania* infection through the induction of alternatively and classically triggered macrophages (Borbón et al. 2019).

The innate immune response versus *Leishmania* infection triggers the onset of the actions of inflammatory monocytes, tissue-resident macrophages, effectors, and efferocytosis (Chaves et al. 2020; Silva et al. 2022). From the earliest steps of *Leishmania* infection, the C–C motif chemokine ligand 2 (CCL2)-C–C chemokine receptor type 2 (CCR2) axis recruits monocytes to the site of infection, as pivotal actors in the innate immunity (van Zandbergen et al. 2006; Peters et al. 2008). The uptake of *Leishmania* by neutrophils also delays their death. According to in vitro data, neutrophil apoptosis is delayed for 2 days via infection of *Leishmania major* (*L. major*), potentially acting as intracellular survival vectors for parasites (van Zandbergen et al. 2004). Apart from the main mechanism, macrophages may affect efferocytose-infected apoptotic neutrophils in the process (van Zandbergen et al. 2006). The AC removal further modifies the phenotype of monocytes to facilitate the infection of this parasite. Efferocytosis accordingly involves the delivery of parasite to the tissue macrophages from apoptotic neutrophils (Vellozo et al. 2021). However, neutrophils not only fail to control parasite burden, but also promote the infection, so they may be a double-edged sword in *Leishmania*-induced infection (Peters et al. 2008; Carreira and da Silva 2021).

The apoptotic neutrophil efferocytosis shows an anti-inflammatory TGF-β signal on neutrophils, inhibiting the efficient elimination of parasites (van Zandbergen et al. 2004). Related data have been also gained with the engulfment of apoptotic neutrophils via macrophages infected with *L. major*, which have generated the prostaglandin of PGE2 and anti-inflammatory mediators of TGF-β (Ribeiro-Gomes et al. 2004).

To study how neutrophil acts in this way, Ribeiro-Gomes et al. developed an infection of *L. major* in mice and extracted the neutrophils, and then incubated them for about 12 h. The culture results showed that DC could capture parasite-bearing and uninfected neutrophils at an extremely low rate, and DC related to parasite-bearing neutrophils was less able to cross-prim CD8 + T cells in comparison with uninfected neutrophils from the same animal. On the opposite side, DC that captures uninfected can help in the cross-priming of CD8 + T cell. Thus, in summary, these findings highlighted the significant performance of efferocytosis to cross-prim during infection (Ribeiro-Gomes et al. 2015). Some studies have further revealed that *Chlamydia pneumoniae*, *Yersinia pestis*, and *L. major*, are engulfed by the human neutrophils, persevere inside the phagosome, and change apoptosis. Neutrophils carrying such living microbes are then engulfed by the human macrophages (van Zandbergen et al. 2004; Peters et al. 2008; Rupp et al. 2009; Spinner et al. 2014). Although it is unclear and merits further study if this can be attributed to the concealment of entry with the aid of efferocytosis, the upregulation of parasitic/bacterial pro-survival factors while in the neutrophil or uncontrolled proliferation in the neutrophil and thus greater primary parasitic or bacterial burden transferred into macrophages or other routes have a role to play in this case (Seyed and Rafati 2019). The co-cultivation of macrophages and microbe-bearing neutrophils results in less pro-inflammatory cytokines, and further anti-inflammatory cytokines, like TGF-β and IL-1 receptor antagonist (RA) (van Zandbergen et al. 2004; Rupp et al. 2009; Spinner et al. 2014).

Accordingly, pathogens employ efferocytosis to penetrate into a host cell. Of note, the outcomes should be assessed in the background of the species of parasite, type and strain of hosts, and the timing of macrophage contact with apoptotic neutrophils as compared to their contact with the parasite. To conclude, it is complicated and context-dependent to state that the efferocytosis of dying neutrophils may lead to harmful or beneficial after-effects for the parasite (Lopes et al. 1995; Cabral-Piccin et al. 2016).

Potential therapeutic interventions via efferocytosis

Currently, several therapeutic interventions have the possibility to influence efferocytosis during pneumonia and other inflammatory diseases of the lungs. These treatments enhance alveolar macrophage efferocytosis, and restore lung homeostasis through anti-inflammatory effects (Papanicolaou et al. 2020; Zheng et al. 2021b). Considering the functions and molecular mechanisms of efferocytosis has opened up many possible routes for therapeutic interventions. There are numerous emerging strategies for utilizing efferocytosis therapeutically, such as utilizing small molecules that target receptors for phosphatidylserine (PS) on phagocytes.

However, the possibility of targeting efferocytosis for therapeutic goals during infections is dependent on pathogens type. One potential approach is using antibodies or small peptides that block different PS receptors during the replicative phases of viral infections to inhibit cellular entry. As proof of concept, blocking PS was highly effective in blocking Zika virus replication in vivo (Song et al. 2021). Another approach could be to enhance the expression of PS receptors during the later stages of enveloped virus infection to help inhibit viral shedding. During the late stages of HIV-1 replication, viral budding and release are associated with the incorporation of PS receptors on HIV-1 virions, and these HIV-1 particles are retained on the plasma membrane, inhibiting viral release (Li et al. 2014; Mehrotra and Ravichandran 2022).

Targeting efferocytosis is also evolving as an interesting prospect in COVID-19 infections. Nowadays, some potential therapeutic interventions that can manipulate the removal of apoptotic cells during other lung inflammatory diseases and pneumonia include statins and glucocorticoids. They reduce inflammation by enhancing the ability of alveolar macrophages to remove apoptotic cells and reform lung homeostasis. Statins function by inhibiting the RhoA pathway to control efferocytosis. Glucocorticoids like Statins interact with the RhoA pathway to improve the removal of apoptotic cells (McCubbrey et al. 2012; Stolberg et al. 2015; Zheng et al. 2021a).

Besides, these therapeutics may increase the risk of infection due to the negative side effects they have, and novel therapies like resolvins and anti-CD47 therapy are needed. Resolvins have been shown to aid in the recovery of lung tissues following disease, particularly RvD1 after Pseudomonas aeruginosa infection (Cham et al. 2020; Gao et al. 2020).

Other studies have further demonstrated that the efferocytosis of apoptotic neutrophils have enhanced the control of *M. tb* in single and *HIV*-co-infected macrophages, indicating that myeloperoxidase (MPO) remains active in the apoptotic neutrophils, and can be harnessed by infected macrophages. This association between the innate immune cells could thereby be a way to fight against *M. tb* infection (Andersson et al. 2020b).

Another example of efferocytosis-mediated host defense happens when particular bacteria, such as some strains of *Klebsiella pneumoniae*, trigger pyroptosis in neutrophils. This point is important to treatment options for bacterial neutralization (Doran et al. 2020a).

The efferocytosis of infected ACs can further help an adaptive immune response against bacteria through the antigen cross-presentation process. This principle originally occurred in vitro by demonstrating that the efferocytosis of *IAV*-infected apoptotic monocytes by DCs had led to the cross-presentation of *IAV* antigens on major histocompatibility complex (MHC) class I and the activation of CD8 + T cells (Albert et al. 1998), although in vivo evidence of this concept has proven to be more challenging.

Challenges and future perspectives

Over the last years, many scientific attempts have been focused on finding out the various aspects of efferocytosis mechanisms. Despite the common mechanism, the details of molecules and processes are not yet fully understood. These complicated procedures may be impaired by extracellular performances, environmental or metabolic alterations, or epigenetic/genetic events. Efferocytosis is thus of utmost importance in numerous fields of biology from autoimmunity and neuroscience to cancer. More importantly, defective efferocytosis is a substantial issue that has received considerable empirical attention until now. Tissue homeostasis can be further lost following inadequate cell clearance, thereby developing various disorders. It also plays a pivotal role in the onset and progression of chronic inflammations, like obesity, cancer, atherosclerosis, heart failure, diabetes, neurodegenerative disorders, and chronic lung disease (Tajbakhsh et al. 2021). Although several key areas of this process have remained untouched, investigating various aspects of efferocytosis can shed light on its physiological and pathophysiological roles, emerging novel therapeutics, or alternative treatments that simultaneously suppress inflammation and promote pathogen clearance.

Discussion

Some microbes, like extracellular bacteria, are efficiently destroyed by phagocytosis, but there is another fate for some other pathogens (Yan et al. 2021). The role of efferocytosis in microbial immunity as a mechanism for infection control is just drawing much attention to itself these days (Ge et al. 2022b). Following the efferocytosis of infected ACs, dying cells produce "find-me" signals, such as chemokines that recruit macrophages and other

phagocytic cells to target sites, along with the accumulation of PS on the exofacial leaflet (Pontejo and Murphy 2021). At the "eat-me" step, the recruited macrophages express specific receptors and bridge molecules that bind to specific ligands on the AC and activate Ras-related C3 botulinum toxin substrate 1 (Rac1), leading to actin reorganization that surrounds the infected AC, and consequently engulfs AC in efferosome (Lam and Heit 2021). Efferosome also undergoes maturation, and merges with lysosomes and endosomes, leading to the degradation of the AC and the intracellular pathogen (Lancaster et al. 2021; Purnama et al. 2021). Alternatively, efferocytosis may allow the pathogen to separate into novel cellular hosts (as a "Trojan Horse" mechanism) (Behar and Briken 2019). In sum, two possibilities have been described for the fate of microbes inhabiting in the dying cells: (a) microbes are trapped behind the membrane from the ACs and cannot reach their host targets (b), microbes have adapted and bypassed the defense mechanism and hijacked it to alternatively survive and spread (Ge et al. 2022b). As reviewed here, the efferocytosis of *IAV* and *M. tb*-infected cells results in pathogen destruction, and that of *Leishmania*-infected neutrophils may enhance the infection. In that case, it should be determined whether efferocytosis can be manipulated to modify the virulence of bacteria or attenuate the unwanted consequences of infection or not. Moreover, it is of utmost importance to consider how efferocytosis is regulated during infection (Doran et al. 2020b).

Against this background, understanding how macrophages, DCs, and neutrophils process pathogens encased within dying infected cells can direct the development of novel therapeutics that simultaneously suppress inflammation and promote pathogen clearance. Since much research until now has investigated the mechanism of efferocytosis in cellular and animal models, and little development is being made in the clinical context (Werfel and Cook 2018; Soehnlein and Libby 2021; Björkegren and Lusis 2022), treatment options with the aim of improving efferocytosis to reduce inflammatory responses and enhance resolution are predicted to occur in the next few years. They can further point to the possible strategies for the use of efferocytosis and its implications to change the course of the disease. Many points should be certainly considered in the future, and all new therapeutic findings can surely lead to the emergence of challenging endeavors based on diverse outcomes of pathogen clearance via efferocytosis; for example, further studies are critically needed to explore the impact of regulating efferocytosis on susceptibility to inflammatory pathologies and the safety of this approach in clinical settings. However, there are many gaps in this field and more studies on this subject are required to provide a better understanding of the host–pathogen interaction.

Conclusion

In this review, there was an attempt to reflect on the critical roles played by efferocytosis in maintaining normal homeostasis, and above all its controversial role in pathogen clearance. Here, an update on the current mechanisms of efferocytosis was provided, and much evidence was presented that many bacterial pathogens could actively inhibit host cell apoptosis and avoid the antibacterial effects of efferocytosis. Generally, both positive and negative consequences of efferocytosis against some pathogens include *M. tb, M. marinum*, *L. monocytogenes*, *CP, KP, IAV*, *HIV*, and *Leishmania* were entirely discussed.

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Declarations

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