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Cellular mechanisms underlying the impairment of macrophage efferocytosis

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ABSTRACT

The phagocytosis and clearance of dying cells by macrophages, a process termed efferocytosis, is essential for both maintaining homeostasis and promoting tissue repair after infection or sterile injury. If not removed in a timely manner, uncleared cells can undergo secondary necrosis, and necrotic cells lose membrane integrity, release toxic intracellular components, and potentially induce inflammation or autoimmune diseases. Efferocytosis also initiates the repair process by producing a wide range of pro-reparative factors. Accumulating evidence has revealed that macrophage efferocytosis defects are involved in the development and progression of a variety of inflammatory and autoimmune diseases. The underlying mechanisms of efferocytosis impairment are complex, disease-dependent, and incompletely understood. In this review, we will first summarize the current knowledge about the normal signaling and metabolic processes of macrophage efferocytosis and its importance in maintaining tissue homeostasis and repair. We then will focus on analyzing the molecular and cellular mechanisms underlying efferocytotic abnormality (impairment) in disease or injury conditions. Next, we will discuss the potential molecular targets for enhanced efferocytosis in animal models of disease. To provide a balanced view, we will also discuss some deleterious effects of efferocytosis.

1. Macrophage efferocytosis

Billions of cells undergo apoptosis each day in an adult. Under normal conditions, these cell corpses are rapidly and efficiently cleared via efferocytosis [1]. Following infectious or sterile injury, more cells are subject to different forms of death. Typically, neutrophils are recruited to the site of injury to conduct microbiocidal function and initiate inflammatory processes; thereafter they become apoptotic and ready to be removed via efferocytosis. From a broader perspective, phagocytosis is a process for ingesting and eliminating particles larger than 0.5 μm in diameter, including microorganisms, cell debris, foreign substances, and dying cells [2,3]. Efferocytosis is a specialized type of phagocytosis, defined as the phagocytosis and clearance of apoptotic, aged, injured, and other forms of dying cells [4,5]. Table 1 summarizes the major differences between phagocytosis of non-cell particles and efferocytosis.

Efferocytosis is performed mainly by professional phagocytes, including macrophages, monocytes, and dendritic cells (DCs), to a lesser extent by non-professional phagocytes, such as epithelial cells, endothelial cells, and fibroblasts, as well as specialized phagocytes, including sertoli cells and retinal pigment epithelial cells [4,6,7]. In the steady state, resident macrophages residing in almost every organ and tissue are the major phagocytes to perform efferocytosis [8]. Tissue resident macrophages are imprinted by their microenvironment and by "physiological" apoptotic cell removal [9,10]. Some tissue resident macrophages have specific names; for example, alveolar macrophages in lungs, microglia in the brain, and Kupffer cells in the liver.

During infection and sterile inflammation, both resident macrophages and recruited macrophages derived from blood monocytes are involved in the clearance of apoptotic cells [11]. Macrophages also undergo reprogramming from early pro-inflammatory to later anti-inflammatory, and eventually to pro-resolving phenotypes. Efferocytosis results in several beneficial consequences: prevention of secondary necrosis and subsequent release of toxic intracellular materials, inhibition of pro-inflammatory cytokine generation, promotion of self-tolerance, and initiation of inflammation resolution and tissue repair by generating pro-reparative factors, including interleukin (IL)−10, transforming growth factor (TGF)-β1, interferon (IFN)-β, prostaglandin (PG) E2, platelet activating factor, and vascular endothelial growth factor (VEGF) C [12–14]. As expected, defective efferocytosis

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Abbreviations

25HC	25-hydroxycholesterol
ABCA1	ATP-binding cassette transporter A1
BAI	brain angiogenesis inhibitor
C1q	complement component 1q
DAMP	damage associated molecular patterns
DCs	dendritic cells
DEL	developmental endothelial locus
Drp1	dynamin-related protein 1
ER	endoplasmic reticulum
ERK	extracellular signal-regulated kinase
Gas6	growth arrest-specific gene 6
GM-CSF	granulocyte-macrophage colony-stimulating factor
HMGB	high mobility group box
IFN	interferon
IL	interleukin
LOX	lipoxygenase
LRP1	low-density lipoprotein-related protein 1
LPS	lipopolysaccharide
LTB4	leukotriene B4
LXR	liver x receptor
MFG-E8	milk fat globule-epidermal growth factor 8
MHC	major histocompatibility complex
MI	myocardial infarction
NETs	neutrophil extracellular traps
PAI	plasminogen activator inhibitor
PD-L1	programmed death-ligand 1
PG	prostaglandin
PPAR	peroxisome proliferator-activated receptor
PPP	pentose phosphate pathway
PS	phosphatidylserine
RAGE	receptor for advanced glycation end products
RXR	retinoid x receptor
S1P	sphingosine-1-phosphate
SIRP	signal regulatory protein
SLC	solute carrier
SPM	specialized pro-resolving mediators
TGF	transforming growth factor
TIM	T cell immunoglobulin mucin
Tregs	regulatory T cells
UCP	uncoupling protein
VEGF	vascular endothelial growth factor

Table 1
The major differences between phagocytosis of non-cell particles and efferocytosis.

	Phagocytosis of non-cell particles	Efferocytosis
Ingestion of	Pathogens, cell debris, and foreign substances	Apoptotic, aged, injured, and other forms of dying cells with exposed eat-me signals
Mainly performed by	Neutrophil, monocyte, macrophage	Professional phagocytes: Macrophage, monocyte, dendritic cell Non-professional phagocytes: Epithelial cell, endothelial cell, fibroblast Specialized phagocytes: sertoli cell, retinal pigment epithelial cell
Receptors	Non-opsonic: Dectin-1, Mincle, MCL, DC-Sign, CD206, MARCO, CD36, SR-BI/II Opsonic: FcRs, complement receptors, α5β1 (CD49e/CD29)	Direct: BAI-1, stabilin-1/2, TIM-1, −3, −4, RAGE, CD14, CD300, LRP1 Indirect: TAMs (Tyro3, Axl, MertK), αvβ3, αvβ5, CD36, CD11b/CD18, CD11c/CD18
Opsonins/bridging molecules	IgG, complement	Gas6, protein S, MFG-E8, C1q, DEL-1, CCN1, thrombospondin-1
Corpse digestion in	Phagolysosome	Phagolysosome
Consequence	inflammation induction	Inflammation resolution

Note: FcRs include FcγRI (CD64), FcγRII (CD32), FcγRIII (CD16), and FcαRI (CD89). Complement receptors consist of CR1 (CD35), CR3 ($\alpha_M\beta2$, CD11b/CD18, Mac-1), and CR4 ($\alpha_V\beta2$, CD11c/CD18, gp190/95).

can cause non-resolving inflammation and autoimmune diseases.

1.1. Efferocytosis process

Efferocytosis involves a sequential cascade of finely tuned events. The efferocytosis process and phagocytic receptors have been reviewed in detail elsewhere [4–6,15–19]. Here, we only present some key steps of efferocytosis (Fig. 1).

Step 1: apoptotic cells release soluble find-me signals, including lysophosphatidylcholine, sphingosine-1-phosphate (S1P), CX3CL1 (fractalkine), and ATP/UTP, which recruit macrophages to the site of cell death by engaging corresponding receptors, including G2A, S1PRs, CX3CR1, and P2Y [20]. Some of the find-me signals also participate in other steps of efferocytosis. For example, S1P can activate macrophage erythropoietin signaling to elevate efferocytosis [21]. CX3CL1 upregulates eat-me signals to enhance apoptotic cell clearance by macrophages [22]. Leukotriene B4 (LTB4) is a potent chemoattractant for neutrophils. Accumulating evidence shows that LTB4 acts as a necrotic “find-me” signal to neutrophils, which amplifies neutrophil recruitment to the injury site [23]. However, LTB4 seems not to affect monocyte infiltration because LTB4 receptor deletion or pharmacological blockage does not affect monocyte recruitment to the injured area [24].
Step 2: apoptotic cells express eat-me signals, such as phosphatidylserine (PS) and calreticulin, on the outer leaflet of plasma membrane, which bind to receptors on macrophages to initiate engulfment. Phagocytic receptors that directly bind to PS include brain angiogenesis inhibitor (BAI)−1, stabilin-1/2, T cell immunoglobulin mucin (TIM-1, −3, −4), receptor for advanced glycation end products (RAGE), CD14, and CD300, whereas the low-density lipoprotein-related protein 1 (LRP1 or CD91) binds to calreticulin [25]. Receptors that indirectly bind to PS include TAM families (Tyro3, Axl, MerTK), αvβ3/5 integrins, CD36, CD11b/CD18, and CD11c/CD18 [26], and these receptors need bridging molecules, such as growth arrest-specific gene 6 (Gas6), protein S, milk fat globule-epidermal growth factor 8 (MFG-E8, lactadherin), complement component 1q (C1q), developmental endothelial locus (DEL)−1, CCN1, and thrombospondin-1. For instance, TAMs rely on Gas6 or protein S, $\alpha_v\beta_{3/5}$ integrins depend on MFG-E8, DEL-1 [27], or CCN1 [28]. CD36 recognizes thrombospondin-1 in association with αv/β3 and αv/β5 integrins [29,30]. C1q can interact with calreticulin-LRP1 on macrophages to facilitate apoptotic cell engulfment [31].

Several possibilities may explain why multiple phagocytic receptors are necessary for efficient efferocytosis. First, multiple phagocytic receptors binding to eat-me signals can accurately distinguish apoptotic cells from live cells with transiently externalized PS expression [16], thus avoiding clearing live cells. Second, receptor expression on

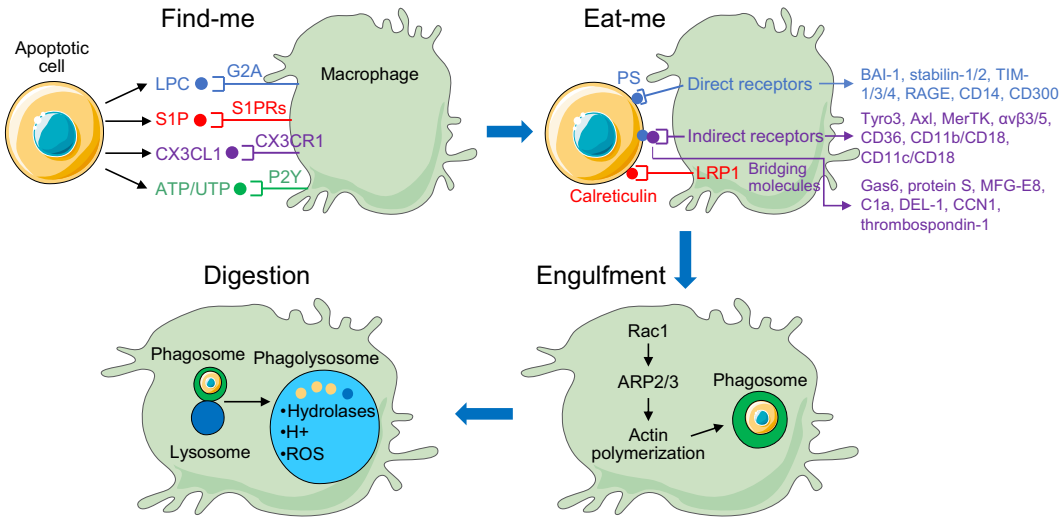

Fig. 1. Efferocytosis process. Efferocytosis involves a sequential cascade of finely tuned events. Step 1: apoptotic cells release soluble find-me signals, including lysophosphatidylcholine (LPC), sphingosine-1-phosphate (S1P), CX3CL1 (fractalkine), and ATP/UTP, which recruit macrophages to the site of cell death by engaging corresponding receptors, including G2A, S1PRs, CX3CR1, and P2Y. Step 2: apoptotic cells express eat-me signals, such as phosphatidylserine (PS) and calreticulin, on the outer leaflet of plasma membrane, which bind to receptors on macrophages to initiate engulfment. Phagocytic receptors bind to PS through direct and indirect ways (via bridging molecules). By contrast, low density lipoprotein-related protein 1 (LRP1) binds to calreticulin. Step 3: following apoptotic cell uptake, activated Rac1 facilitates actin polymerization and phagocytic cup formation via activating actin-related protein 2/3 (ARP2/3) complex. Step 4: phagosomes fuse with lysosomes to form phagolysosomes, where corpse cargo is degraded through hydrolases, high acidity, and reactive oxygen species (ROS) associated mechanisms. Images of cells and organelles are from Servier Medical ART (https://smart.servier.com).

macrophages is organ- and context-dependent. For example, MFG-E8 is important for apoptotic cell removal by inflammatory macrophages. In contrast, TIM-4 is essential for homeostasis in peritoneal macrophages [32]. MerTK functions as a tolerogenic receptor in resting macrophages and during immunosuppression, while Axl is activated by pro-inflammatory stimuli [33]. Third, multiple receptors may be required to perform sophisticated cellular processes during efferocytosis [16]. For example, TIM-4 acts as a tethering receptor for binding between apoptotic cells and peritoneal macrophages, while MerTK functions as a tickling receptor to mediate engulfment [34]. BAI-1 contributes to the formation and transport of phagosomes, whereas TIM-4 is implicated in phagosome stabilization [35].

Step 3: engulfed (or eaten) cells induce signaling activation within macrophages, leading to actin polymerization and phagosome formation. Following uptake of apoptotic cells, macrophage cytoskeletons must be rearranged to internalize them. Rho GTPases are essential regulators of actin rearrangement. Rac1 activation contributes to actin polymerization and phagocytic cup formation around internalized apoptotic cells via activating actin-related protein 2/3 complex [36]. Myosin light chain phosphorylation facilitates actomyosin contraction [37] and is also implicated in phagosome formation and efferocytosis [38]. Rac1 can be activated by the ELMO/DOCK180 complex [39] or GULP1 [40], depending on the receptors engaged. In contrast, RhoA activation negatively regulates efferocytosis by promoting stress fiber formation [41] and inhibiting Rac1 activity via activating ROCK [42].
Step 4: phagosomes fuse with lysosomes to form phagolysosomes, a process known as phagosome maturation. This process is governed by Rab GTPase family of proteins, including Rab5 and Rab7 [4]. The phagolysosome utilizes several mechanisms to degrade apoptotic cell corpses, such as hydrolases (e.g. cathepsins, DNase II), high acidity (pH 4.5–5.0), and reactive oxygen species.

1.2. Metabolic reprogramming in efferocytotic macrophages

When a macrophage ingests an apoptotic cell, it almost doubles its cellular contents. More often, one macrophage successively engulfs multiple apoptotic cells. Therefore, efferocytotic macrophages face a high burden of removing apoptotic cell cargo and digesting them, and both require energy. Following cargo degradation, macrophages either utilize these metabolites or efflux them to maintain metabolic homeostasis and prepare for subsequent efferocytosis [5,43]. It has been shown that the uptake of apoptotic neutrophils facilitates macrophage loss of phagocytosis and consequently their transition from $CD11b^{high}$ to $CD11b^{low}$ phenotype, featured by reduced arginase 1 and increased 12/15-lipoxygenase (LOX) expression [44]. In general, pro-inflammatory macrophages utilize glycolysis for energy metabolism, while pro-reparative macrophages exhibit high levels of oxidative phosphorylation. Disturbing the metabolism affects macrophage functions, including efferocytosis, indicating the close integration between metabolism and cell function [45].

Efferocytosis induces a specific solute carrier (SLC) program to facilitate glucose transport and glycolysis [46]. SLC2A1 (also known as GLUT1) is upregulated early during efferocytosis and mediates glucose uptake and glycolysis, which contributes to actin polymerization. SLC16A1 is upregulated after corpse uptake and increases lactate release to extracellular space, where lactate exerts anti-inflammatory roles (Fig. 2A). Interestingly, lactate released by activated bone marrow neutrophils induces their mobilization, exerting pro-inflammatory roles [47]. Therefore, the pro- or anti-inflammatory feature of lactate may depend on its cellular source and the context it encounters.

During efferocytosis, the macrophage takes up arginine and ornithine from apoptotic cells, which are converted to putrescine. Putrescine augments continual efferocytosis by enhancing Rac1 activation (Fig. 2B) [48]. Apoptotic cell-derived methionine also promotes efferocytosis through epigenetic inhibition of the extracellular signal-regulated kinase (ERK) 1/2 phosphatase Dusp4 [49]. In addition, efferocytosis triggers endocytic import of polyamines (spermidine and spermine) via Rac1/actin/PI3K signaling, and imported polyamines suppress the production of pro-inflammatory cytokines (Fig. 2B) [50].

The engulfment of apoptotic cells upregulates uncoupling protein (UCP) 2, which acts to lower the mitochondrial membrane potential and promotes efferocytosis (Fig. 2C) [51]. Inhibition of UCP2 blocks TIM-4 mediated efferocytosis [51], indicating that UCP2 acts as downstream of TIM-4 associated engulfment. Thus, the mitochondrial potential

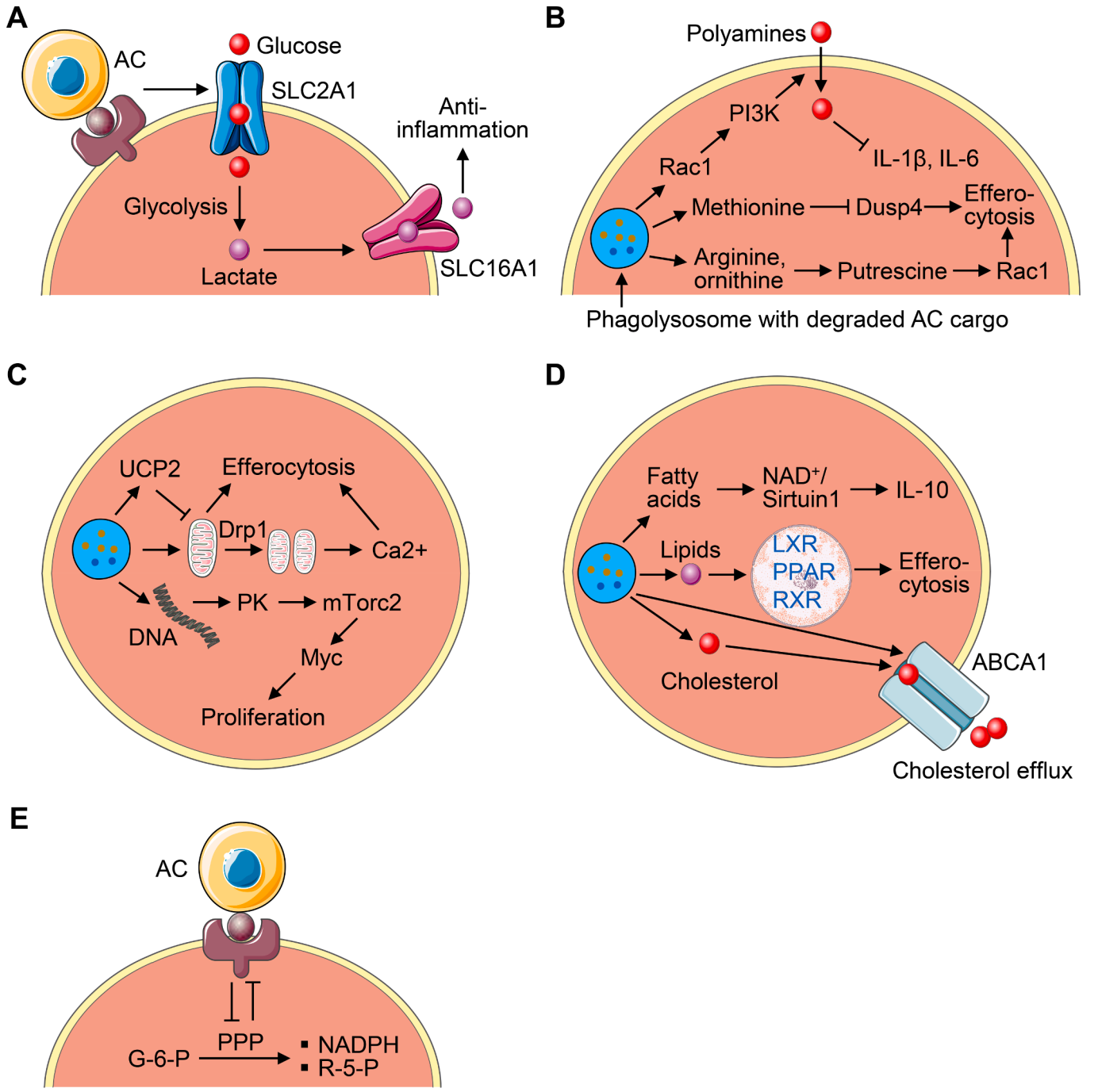

Fig. 2. Metabolic reprogramming in efferocytotic macrophages. (A) Apoptotic cell (AC) uptake upregulates SLC2A1 expression to increase glucose uptake and glycolysis, which generates lactate. Lactate is exported to the extracellular environment via SLC16A1, where it exerts anti-inflammatory effects. (B) Arginine and ornithine derived from apoptotic cells are metabolized to putrescine, which activates Rac1 and enhances efferocytosis. Apoptotic cell-derived methionine inhibits Dusp4 to upregulate efferocytosis. In addition, efferocytosis triggers endocytic import of polyamines via Rac1-associated pathway, and polyamines inhibit the production of IL-1β and IL-6. (C) Apoptotic cell engulfment upregulates uncoupling protein (UCP) 2, which promotes efferocytosis by inhibiting mitochondrial membrane potential. Apoptotic cell uptake triggers dynamin-related protein 1 (Drp1)-induced mitochondrial fission, which facilitates efferocytosis via regulating cytoplasmic Ca2+ release. Apoptotic cell-derived nucleotides activate the DNA-PK-mTorc2-Myc pathway to stimulate macrophage proliferation. (D) Apoptotic cell-derived fatty acids activate NAD+/Sirtuin1 pathway to upregulate IL-10 production. Lipids generated from apoptotic cells activate nuclear receptors, which promote efferocytosis by increasing the expression of phagocytic signaling molecules. Apoptotic cells induce ABCA1 expression to mediate cholesterol efflux. (E) Through the pentose phosphate pathway (PPP), the metabolism of glucose 6-phosphate (G-6-P) produces NADPH and ribose-5-phosphate (R-5-P). Apoptotic cell engulfment inhibits PPP metabolism; in turn, PPP inhibits efferocytosis. Images of cells and organelles are from Servier Medical ART (https://smart.servier.com).

modulates engulfment capacity. Apoptotic cell uptake triggers dynamin-related protein 1 (Drp1)-induced mitochondrial fission. Mitochondrial fission enables the release of endoplasmic reticulum (ER) Ca2+ into the cytoplasm, where it allows phagocytosis of a second apoptotic cell by mediating vesicular trafficking (Fig. 2C) [52].

Efferocytosis also leads to increased cellular fatty acids, which fuel mitochondrial respiration and activate an NAD^+/Sirtuin1/IL-10 signaling cascade (Fig. 2D). This metabolic signaling pathway in macrophages facilitates myocardial repair post-myocardial infarction (MI) [53].

Apoptotic cell-derived lipids activate the nuclear receptor family of transcriptional regulators, including liver x receptor (LXR), peroxisome proliferator-activated receptor (PPAR), and retinoid x receptor (RXR) [54,55]. The activation of these receptors increases efferocytosis by enhancing the expression of efferocytosis receptors, bridging molecules, intracellular engulfment signaling molecules, and anti-inflammatory mediators [15,56–58]. In addition, apoptotic cells induce ATP-binding cassette transporter A1 (ABCA1) expression via the BAI-1/ELMO1/Rac1 pathway [59]. ABCA1 mediates cholesterol efflux and decreases intracellular cholesterol load in macrophages (Fig. 2D). Cholesterol can also be hydrolyzed by the lysosomal acid lipase to generate 25- and 27-hydroxycholesterol, which further activate LXR for cholesterol efflux [60].

Apoptotic cell-derived nucleotides can induce efferocytotic macrophages to proliferate via the DNA-PK-mTorc2-Myc pathway, which expands the pool of resolving macrophages and promotes inflammation resolution and atherosclerosis regression (Fig. 2C) [61]. These findings may implicate new strategies to treat non-resolving inflammatory diseases.

The pentose phosphate pathway (PPP) generates NADPH for the synthesis of fatty acid, cholesterol, and reduced glutathione and ribose-5-phosphate for nucleotide synthesis. Pro-inflammatory macrophages exhibit upregulated PPP activity, while anti-inflammatory macrophages show decreased PPP activity [45]. Consistently, a recent study shows that efferocytotic macrophages display reduced PPP metabolism, and activation of PPP with pharmacological agonist AG1 inhibits efferocytosis (Fig. 2E) [62]. This indicates that PPP negatively regulates macrophage clearance of apoptotic cells.

In summary, the efferocytosis process involves complex signaling interaction between apoptotic cells and phagocytes. Moreover, apoptotic cell-derived metabolites affect efferocytosis.

2. Cellular mechanisms of macrophage efferocytosis impairment

Macrophage efferocytosis is indispensable for homeostasis maintenance and tissue repair after infection or sterile injury. Efferocytosis defects are involved in the development and progression of a variety of diseases. In the following section, we will summarize the cellular mechanisms underlying the impairment of macrophage efferocytosis mainly using infectious and chronic lung diseases as examples (Table 2).

2.1. Downregulation of eat-me signals

During apoptosis, PS is exposed from the inner leaflet to the outer leaflet of plasma membrane [63], and then PS binds to phagocytic receptors on macrophages for clearance. One study shows that *Klebsiella pneumoniae* can prevent PS externalization on neutrophils, thus impairing efferocytosis [64]. Calreticulin is localized in the ER of live cells. It is also expressed on the surface of apoptotic cells, serving as an eat-me signal that binds to macrophage LRP1 [25]. Dead cells in atherosclerotic plaque lesions express lower calreticulin levels [65]. Cdkn2b$^{-/-}$ Apoe$^{-/-}$ mice exhibit lower calreticulin levels than Cdkn2b$^{+/+}$Apoe$^{-/-}$ counterparts, and apoptotic cells from Cdkn2b$^{-/-}$ mice are not efficiently cleared by neighboring macrophages [65]. When fed a Western diet, Cdkn2b$^{-/-}$ mice show an increase in lesion size and necrotic core size, implying that lower calreticulin on apoptotic cells may impair macrophage efferocytosis and thus contribute to atherosclerosis progression. Whether reduced PS and calreticulin exposure on apoptotic cells contributes to efferocytosis defects in other diseases needs to be investigated.

Table 2
Cellular mechanisms of macrophage efferocytosis defects.

- v Downregulation of eat-me signals: PS, calreticulin
- v Upregulation of don't eat me signals: CD47, PAI-1, SIRPα
- v Downregulation of bridging molecules: MFG-E8
- v Regulation of phagocytic receptors

- MerTK cleavage
- Axl reduced expression
- Inhibition of LRP1 transport to cell surface, LRP1 cleavage, and internalization
- CD36 reduced expression and cleavage
- αvβ3 and αvβ5 integrins cleavage
- αvβ5 and RAGE binding to HMGB1, αvβ5 and MerTK binding to histone H3

2.2. Upregulation of don't eat-me signals

Healthy cells express high levels of don't eat-me signals to prevent efferocytosis even when eat-me signals are exposed. Don't eat me signals include programmed death-ligand 1 (PD-L1), CD47, CD31, CD24, and major histocompatibility complex (MHC)-I, which bind to corresponding inhibitory receptors, including PD, signal regulatory protein (SIRP) α, CD31, Siglec10, and LILRB1 respectively [4]. The engagement between don't eat-me signals and their receptors activates intracellular inhibitory signaling (e.g. SHP1 and SHP2) and results in the negative regulation of actin rearrangement and efferocytosis [16].

CD47 binding to thrombospondin-1 has been shown to regulate blood pressure and suppress nitric oxide signaling in endothelial cells [66]. CD47 also binds to SIRPα on macrophages to inactivate myosin assembly, prevent cytoskeletal rearrangement, and inhibit efferocytosis [67]. Neutrophil engulfment of methicillin-resistant *Staphylococcus aureus* induces CD47 expression [68], which may prevent neutrophils to be cleared by efferocytosis. Surfactant proteins A and D inhibit alveolar macrophage efferocytosis via SIRPα/SHP1/RhoA dependent pathways [69]. This may partially explain why alveolar macrophages are less efferocytotic than other resident macrophages. Clinical evidence shows that nonsteroidal pain killers increase the incidence of MI and re-admission events in heart failure patients [70,71]. However, the underlying mechanisms are unclear. One study reveals that subacute treatment of mice with carprofen promotes resolution impairment after MI, which is associated with CD47 and SIRPα upregulation to defer efferocytosis [72].

Plasminogen activator inhibitor (PAI)−1, an inhibitor of fibrinolysis, is known to exert pro-inflammatory roles by enhancing lipopolysaccharide (LPS)-triggered neutrophil activation [73] and facilitating neutrophil recruitment [74]. Viable neutrophils lacking PAI-1 demonstrate elevated ingestion by macrophages, indicating that PAI-1 can serve as a don't eat-me signal. PAI-1 interacts with calreticulin on viable cells to prevent efferocytosis. Apoptotic neutrophils exhibit reduced PAI-1 expression, which allows calreticulin to bind to LRP1 and induce efferocytosis [75]. PAI-1 levels are increased in acute lung injury [76], which may impair efferocytosis and contribute to non-resolving inflammation. Future studies are warranted to determine how other don't eat me signals, including PD-L1, CD31, CD24, and MHC-1, inhibit macrophage efferocytosis in disease models.

2.3. Downregulation of bridging molecules

MFG-E8 acts as a potent bridging molecule that connects apoptotic cells to macrophages for clearance. It is mainly produced by macrophages and DCs. MFG-E8 levels in the spleen and liver are significantly decreased after cecal ligation and puncture-induced sepsis, which is associated with impaired apoptotic cell removal and increased mortality [77,78]. Lung MFG-E8 levels are reduced after intestinal ischemia/reperfusion and involved in lung injury [79]. Whether other bridging molecules are decreased after infection or sterile injury remains to be elucidated.

2.4. Regulation of phagocytic receptors

MerTK is one of the most established phagocytic receptors. MerTK deficient mice develop a systemic lupus erythematosus (SLE)-like autoimmune disease, indicating an essential role for MerTK in clearing

"physiological" apoptotic cells [80]. MerTK cleavage not only negatively affects efferocytosis, but also impairs MerTK-dependent production of specialized pro-resolving mediators (SPM) and anti-inflammatory cytokines by macrophages [81]. ADAMs are a family of membrane-anchored proteins that participate in cytokine, growth factor, and glycocalyx shedding [82]. Under inflammatory conditions, upregulated ADAM17 cleaves cell surface MerTK, resulting in downregulation of cell surface MerTK and upregulation of soluble MerTK, and subsequent impaired efferocytosis [83]. This also happens when bone marrow-derived macrophages are exposed to fine particulate matter ($PM_{2.5}$) [84]. In diabetic mice, increased ADAM9 may cleave MerTK, causing defective efferocytosis of apoptotic cardiomyocytes [85]. Further, soluble MerTK can bind to bridging proteins (e.g. Gas6 and protein S), which impedes their association with surface MerTK [86]. Plasma soluble MerTK is upregulated in a mouse model of endotoxemia induced by LPS [83]. Preventing MerTK cleavage using MerTK cleavage-resistant mice improves resolution of sterile peritonitis and decreases lung damage induced by hindlimb ischemia/reperfusion [81]. Diminished Axl expression by airway macrophages is associated with defective efferocytosis in asthma patients [87]. Soluble Axl in sputum is elevated in patients with asthma compared with controls [87]. However, whether Axl is cleaved by ADAM17 or ADAM9 in these conditions are unknown.

Rab43 mediates LRP1 transport from the cytoplasm to the cell surface. High mobility group box (HMGB) 1 inhibits Rab43 expression, which decreases LRP1 surface levels and inhibits efferocytosis [88]. LRP1 can also be cleaved by ADAM17 [89] or internalized [90], thus impairing engulfment of apoptotic cells. In addition to being a long-chain fatty acid transporter, CD36 functions as a phagocytic receptor [91]. CD36 binds to oxidized PS to promote engulfment [92]. It has been shown that exogenous CXCL4 infusion inhibits macrophage phagocytosis of apoptotic cells by inhibiting CD36 expression, thus exacerbating left ventricular dilation and mortality after MI [93]. Pneumonia-causing *Francisella novicida* is able to suppress CD36 expression and impair efferocytosis, leading to the accumulation of necrotic tissue and sustained infection [94]. It is worth noting that CD36 can be cleaved by ADAM17 [95]. In addition, some integrins, especially αvβ3 and αvβ5, also act as indirect phagocytic receptors, with MFG-E8 as the bridging molecule. Neutrophil elastase in neutrophil extracellular traps (NETs) cleaves αvβ3/αvβ5 integrins to impair efferocytosis, which exacerbates sepsis [96].

HMGB1 is a nuclear DNA binding protein and assists in DNA replication, repair, and transcription. Following injury, it can be released into the extracellular milieu, acting as a damage associated molecular patterns (DAMP). HMGB1 levels in plasma and tissues are elevated in both uncomplicated pneumonia and pneumonia with severe sepsis [97]. Although controversy exists regarding its pro-inflammatory property, HMGB1 is able to associate with LPS [98], cytokines [99], and DNA [100] to enhance their pro-inflammatory activity. In addition, HMGB1 is shown to suppress efferocytosis not only by binding to apoptotic cells [101] or αvβ5 integrin and RAGE on macrophages [102,103], but also by inhibiting the Rab43 controlled cell surface transport of LRP1 [88]. During the apoptotic process, HMGB1 is oxidized, which disarms this DAMP [104].

Histones are integral components of nucleosomes and play essential roles in regulating gene transcription, chromatin condensation, and DNA repair. Plasma histone levels are significantly increased in sepsis and induce endothelial barrier dysfunction and blood brain barrier opening [105–107]. Histone H3 inhibits efferocytosis through binding to both αvβ5 integrin and MerTK, thus interrupting their interaction with bridging molecules [108]. Activated protein C, which degrades histone, can abrogate the inhibitory effects of histone H3 on efferocytosis *in vitro* and *in vivo* [108].

In summary, efferocytosis defects involve multiple mechanisms from upstream eat-me and don't eat me signal changes to downstream phagocytic receptor alterations. Pro-inflammatory mediators and DAMPs generated during infection and tissue injury can affect these mechanisms to regulate efferocytosis.

3. Potential targets to enhance macrophage efferocytosis

Since macrophage efferocytosis defects are involved in the pathogenesis of a variety of diseases, lots of efforts have been made trying to correct efferocytosis impairment and/or increase efferocytosis. In this section, we present some targets to nonspecifically enhance efferocytosis and improve outcome in animal disease models (Table 3). Strategies that can specifically elevate macrophage efferocytosis need to be developed.

3.1. Administration of apoptotic cells

Accumulating evidence has shown that apoptotic cells exhibit potent immunomodulatory and anti-inflammatory properties, which is associated with the enhancement of efferocytosis and the induction of regulatory T cells (Tregs) [109]. Administration of apoptotic leukocytes stimulates allogeneic bone marrow engraftment in mice [110] and protects against acute graft-versus-host disease in patients [111]. Apoptotic cell instillation alleviates inflammation and fibrosis induced by bleomycin [112]. This is associated with the increase of efferocytosis via upregulating PPARγ, phagocytic receptors (e.g. CD36), and pro-reparative factors (e.g. TGF-β, IL-10, and hepatocyte growth factor) [112]. In a clinical trial, septic patients infused with apoptotic cells show better survival, rapid resolution of organ dysfunction, and short hospital stays [113].

Delayed neutrophil apoptosis contributes to nonresolving inflammation in a wide range of diseases, including sepsis [114], acute respiratory distress syndrome [115], and MI [116]. Activation of CD300a on neutrophils promotes their apoptosis, which increases their clearance by efferocytosis and leads to the resolution of inflammation [117]. Promoting neutrophil apoptosis, therefore, may represent a novel way to improve efferocytosis.

Table 3
Potential targets to enhance macrophage efferocytosis.

Targets	Mechanisms
Apoptotic cell Administration	Upregulation of PPARγ, phagocytic receptors, and pro-resolving factors
Pro-reparative factors	Facilitation of neutrophil apoptosis, prevention of MerTK cleavage, promotion of calreticulin transport to cell surface and apoptotic cell binding to macrophages, as well as induction of Gas6 secretion and SPM production
Tregs	Treg-secreted IL-13 induces IL-10 production by macrophages, which activates Rac1 via Val1
Bridging molecules: DEL-1, MFG-E8	Promotion of apoptotic cells binding to phagocytic receptors on macrophages
GM-CSF	Upregulation of Rab5 and Rab7 expression and Rac1 activity to enhance cargo degradation, MFG-E8 induction
Nuclear receptor agonists	Upregulation of phagocytic receptors and bridging molecules
Erythropoietin	PPARγ activation
Plasminogen and plasmin	Annexin 1 upregulation to promote neutrophil apoptosis and PS binding to phagocytic receptors
MEK1/2 inhibitors	MerTK and Tyro3 upregulation
P38 inhibitors	TIM-4 upregulation
Rab11a inactivation	Inhibition of ADAM17 translocation from the cytoplasm to the cell surface, which prevents CD36 cleavage
Statins	Inhibition of CD47 expression and RhoA activation
Glucocorticoids	MerTK and Rac1 activation, SIRPα downregulation, MFG-E8 and IFN-β induction
AMPK agonist	Rac1 activation, RhoA inhibition

3.2. Pro-reparative factors

SPMs are synthesized from essential fatty acids by 5-, 12-, 15-LOX and cyclooxygenase 1 and 2. Macrophages are the major source of SPMs, which consist of lipoxins, D-series and E-series resolvins, protectins, and maresins. SPMs inhibit neutrophil recruitment, promote neutrophil apoptosis, macrophage efferocytosis, and tissue repair, including ischemic myocardial repair [118]. Supplementation with docosahexaenoic acid dominates splenocardiac resolving phase with SPM biosynthesis in MI setting [119]. Apoptotic neutrophils or extracellular vesicles from apoptotic neutrophils induce SPM synthesis by macrophages via providing SPM precursors [30,120]. Resolvin D1 can prevent senescent cell-induced MerTK cleavage and promote efferocytosis, thus mitigating lung injury [121,122]. It also activates the GTPase Cdc42 to mobilize the ER and release calreticulin to necroptotic cell surface for engulfment [123]. Resolvin D1 activates the inflammation resolution process and improves cardiac function post-MI [124]. On the contrary, lack of SPM receptor lipoxin A4/formyl peptide receptor 2 [125] or SPM synthesis enzyme arachidonate 5-LOX causes nonresolving inflammation after MI [126]. Aging dysregulates D- and E-series resolvins following MI [127], thus promoting nonresolving inflammation.

IL-4 can induce Gas6 production in alveolar macrophages to increase efferocytosis in LPS-induced acute lung injury [128]. IFN-β is a novel and potent pro-resolving factor (Fig. 3). Using IFN-β deficient mice and blocking antibodies, it was shown that endogenous IFN-β promotes neutrophil apoptosis, macrophage efferocytosis, and reprogramming toward IL-10 production [13]. IFN-β, at least in part, mediates the pro-resolving effect of galectin-1 in zymosan A-induced peritonitis [129]. IFN-β also regulates SPM production to promote the resolution of acute lung inflammation [130]. Further, exogenous IFN-β administration accelerates the resolution of *E. coli* pneumonia [13] and post-septic acute respiratory distress syndrome in mice [131]. Annexin A1 can be exported from the cytosol of apoptotic cells to the outer leaflet of plasma membrane, where it colocalizes with PS and mediates PS binding to phagocytic receptors [132]. During *M. tuberculosis* infection, annexin A1 mediates DC cross-presentation that enhances efferocytosis in DCs [133]. Whether this mechanism described in DCs is efficient in macrophages remains to be determined. Moreover, annexin A1 is able to enhance neutrophil apoptosis by promoting the degradation of anti-apoptotic protein Mcl-1 [134, 135]. In summary, administration of exogenous pro-resolving factors can increase efferocytosis and promote inflammation resolution and tissue repair.

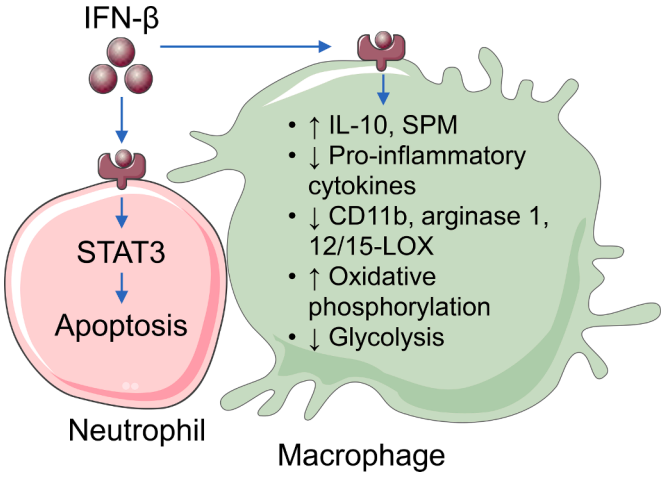

Fig. 3. The molecular mechanisms of INF-β regulation of efferocytosis. IFN-β can directly induce neutrophil apoptosis by activating STAT3. IFN-β also enhances macrophage efferocytosis and triggers macrophage reprogramming, characterized by increased generation of IL-10 and specialized pro-resolving mediators (SPM), inhibition of pro-inflammatory cytokine production, phenotype conversion from $CD11b^{high}$ to $CD11b^{low}$ cells (lower arginase 1 and 12/15-lipoxygenase (LOX)), as well as increased oxidative phosphorylation and reduced glycolysis. Images of cells are from Servier Medical ART (https://smart.servier.com).

The uptake of apoptotic cells by macrophages increases the biosynthesis of pro-reparative factors, which, in a feed-forward manner, further promotes efferocytosis. Secretome secreted by macrophages after efferocytosis, named as SuperMApo, has been shown to increase the efferocytotic capacity of intestinal epithelial cells [136]. Injection of SuperMApo promotes resolution of inflammation and wound healing in arthritis and inflammatory bowel disease [136,137]. The beneficial effects are partially mediated by pro-reparative factors, such as TGF-β, insulin like growth factor-1, and VEGF [136].

3.3. Tregs

As immunosuppressive cells, Tregs are shown to increase macrophage efferocytosis. Tregs secrete IL-13, which stimulate IL-10 production in macrophages. In an autocrine-paracrine manner, IL-10 induces Val1, which activates Rac1 to promote apoptotic cell engulfment [138]. Expansion of Tregs improves efferocytosis in mouse atherosclerosis [138]. In turn, efferocytosis increases Treg expansion in a TGF-β dependent manner [139].

3.4. Bridging molecules

DEL-1 binds to apoptotic cells through its discoidin I-like domains and αvβ3 on macrophages through the RGD site in its second EGF-like repeat. Thus, DEL-1 can serve as a bridging molecule that connects apoptotic cells with macrophages to enhance efferocytosis [27]. DEL-1 is also a pro-resolving factor that contributes to clearance of inflammation. DC-derived exosomes containing MFG-E8 are shown to alleviate septic injury [77], and recombinant MFG-E8 administration attenuates remote organ injury induced by intestinal ischemia/reperfusion [79]. Thus, bridging molecule supplementation represents a promising approach to enhance efferocytosis.

3.5. Granulocyte-macrophage colony-stimulating factor (GM-CSF)

GM-CSF is indispensable for the development and maintenance of alveolar macrophages [140,141]. During efferocytosis, apoptotic cell cargo is transported from Rab5 to Rab4 and Rab11 domains for recycling, while from Rab5 to Rab7 for degradation purposes [142]. GM-CSF upregulates the mRNA expression of Rab5 and Rab7 and Rac1 activity in alveolar macrophages, likely enhancing cargo degradation. Exposure to second-hand cigarette smoke decreases efferocytosis of alveolar macrophages, which can be rescued by GM-CSF administration [142]. GM-CSF treatment protects second-hand cigarette smoke-exposed mice from influenza [142]. GM-CSF may also increase efferocytosis via MFG-E8 [143].

3.6. Nuclear receptor agonists

Activation of nuclear receptors has been shown to upregulate the expression of engulfment receptors and bridging molecules [56,144], thus promoting efferocytosis. LXR agonists are able to increase the efferocytotic receptor BAI-1 in plasmacytoid DCs [145]. *In vitro*, LXR agonist GW3965 pretreatment enhances macrophage efferocytosis [56]. Not surprisingly, GW3965 treatment alleviates disease progression in a mouse model of lupus-like autoimmunity [56]. Recombinant erythropoietin increases efferocytosis and promotes inflammation resolution in peritonitis in a PPARγ-dependent manner [146]. 25-hydroxycholesterol (25HC), an agonist for LXR, is induced in macrophages encountered with apoptotic cells. 25HC deficiency impairs efferocytosis and resolution of lung inflammation induced by LPS [147]. Whether supplementation of exogenous 25HC is beneficial to acute lung injury warrants

further investigation.

3.7. Plasminogen/plasmin

Plasminogen, synthesized by the liver, is the proenzyme of plasmin, which is the major enzyme for thrombolysis. In addition, plasminogen/plasmin are involved in regulating inflammation [148]. Treatment with plasminogen/plasmin increases neutrophil apoptosis and macrophage efferocytosis in LPS- or zymosan- induced peritonitis, the mechanism of which is associated with annexin A1 upregulation [149].

3.8. MEK1/2 and p38 MAPK inhibitors

The MAPKs MEK1 and MEK2 control downstream effector molecules ERK1 and ERK2, which are implicated in regulating inflammation. MEK1/2 inhibition attenuates systemic inflammatory responses and multiple organ injury in murine sepsis [150,151]. We have previously shown that MEK1/2 inhibitors exert potent anti-leakage effects in vascular endothelial cells during inflammation [152]. Additionally, MEK1/2 inhibition increases macrophage efferocytosis via the upregulation of phagocytotic receptors MerTK and Tyro3 and suppresses lung inflammation induced by LPS [151]. Reduced TIM-4 expression in elderly individuals is associated with delayed resolution of inflammation. Administering an p38 inhibitor to the elderly rescues TIM-4 expression and enhances macrophage efferocytosis, thus rejuvenating the resolution phase to the levels of younger people [153].

3.9. Rab11a inactivation

The small GTPase Rab11a plays important roles in endocytic membrane recycling. Rab11a activation triggers FcγR-mediated internalization of IgG-opsonized particles [154]. On the contrary, silencing Rab11a in macrophages significantly increases the efferocytosis of apoptotic neutrophils [155]. This is associated with the inhibition of ADAM17 translocation from the cytoplasm to the cell surface, which prevents CD36 cleavage. In mice challenged with LPS, intratracheal instillation of Rab11a-depleted macrophages increases the number of macrophages engulfing apoptotic neutrophils and ameliorates acute lung injury [155].

3.10. Commonly used medications that enhance efferocytosis

Several commonly used medications can elevate macrophage efferocytosis. Statins augment macrophage efferocytosis by inhibiting CD47 expression and RhoA activation [156–158]. Glucocorticoids increase macrophage efferocytosis, which is dependent on MerTK and Rac1 activation and downregulation of the inhibitory receptor SIRPα [159–162]. Glucocorticoids also induce MFG-E8 to enhance efferocytosis [163]. Instead of being released into the extracellular milieu, MFG-E8 is immediately bound after release to integrin receptors expressed by the cells that produce MFG-E8. IFN-β probably partially mediates the anti-osteoclastic and pro-efferocytotic effects of glucocorticoids [164]. However, glucocorticoids often cause immunosuppression [165], which increases a risk for secondary infection. Therefore, the benefit and risk evaluation of glucocorticoid treatment needs to be considered. Ingestion of apoptotic cells by macrophages increases AMPK activity; in turn, AMPK activation enhances the efferocytotic capability by promoting Rac1 activation and cytoskeletal reorganization while inhibiting RhoA activation [166]. *In vitro*, AMPK activation in macrophages improves efferocytosis and NETs clearance [115]. AMPK activation also enhances neutrophil phagocytosis and bacteria killing in a mouse model of peritonitis [167]. It is likely that the AMPK agonist metformin represents a new strategy to rescue efferocytosis defect.

4. Undesirable effects of macrophage efferocytosis

Although rescuing macrophage efferocytosis defects has been shown to be beneficial in a wide range of inflammatory and autoimmune diseases, some studies demonstrate deleterious effects. Viable cells subject to sublethal stimuli may expose eat-me signals, leading to their clearance via efferocytosis. For instance, MerTK or MFG-E8 promotes long-term functional motor deficits and brain atrophy after stroke through phagocytosing viable neurons [168]. PGE2 produced by alveolar macrophages during efferocytosis suppresses phagocytosis and bacterial killing [169,170], thus posing a risk for secondary infection. Macrophage engulfment of *M. tuberculosis*-infected necrotic neutrophils promotes bacteria growth [171]. Enhanced efferocytosis by glucocorticoids inhibits pulmonary pneumococcal clearance in mice [172]. Repetitive intrapulmonary administration of apoptotic alveolar epithelial cells causes lung fibrosis through CD36-dependent efferocytosis [173]. Efferocytotic phagocytes can secrete a plethora of pro-reparative factors, including TGF-β1 and IL-10. Though being pro-reparative, TGF-β1 can be pro-fibrotic if unchecked [174]. That might partially explain the pro-fibrotic role of efferocytosis. In contrast, IL-10 is both pro-reparative and anti-fibrotic [175]. Phagocyte efferocytosis of dying tumor cells activates NLRP3-dependent inflammasome signaling to induce IL-1β secretion, which facilitates tumor growth [176]. These findings indicate that in addition to beneficial homeostatic and pro-reparative functions, efferocytosis has the undesirable potential to promote disease progression.

5. Conclusions

Macrophage efferocytosis is a fundamental biological process for the elimination of unwanted cells and is crucial for maintaining homeostasis and promoting tissue repair after injury or infection. Impaired macrophage efferocytosis contributes to the development and progression of a wide array of diseases. Some targets that nonspecifically enhance macrophage efferocytosis have been shown to promote inflammation resolution and tissue recovery in animal disease models. However, it is important to keep in mind that excessive efferocytosis is deleterious, which can potentially damage healthy cells, inhibit bacteria phagocytosis, cause tissue fibrosis, and promote tumor growth. Efferocytosis should be kept at an appropriate level to exert beneficial roles while inhibiting detrimental effects. Current strategies that can augment macrophage efferocytosis are highly non-specific. It is hard to quantify to what extent these beneficial effects are due to the improvement of efferocytosis, per se. Thus, there is a need to develop approaches that can specifically target macrophage efferocytosis. To achieve that goal, increased understanding of the molecular and cellular mechanisms of macrophage efferocytosis is warranted. Efferocytotic macrophages exhibit dramatic metabolic reprogramming, and cell metabolism is known to affect various macrophage functions. As such, targeting macrophage metabolism may offer a novel means to manipulate efferocytosis.

In addition to rescuing or enhancing efferocytosis, we can harness the efferocytotic macrophages. Resolution therapy is a novel approach based on the use of pro-resolving mediators to accelerate resolution of inflammation [30]. SuperMApo, the secretome of efferocytotic macrophages, contains multiple pre-resolving factors, such as TGF-β, IL-10, IL-1RA, and VEGF [30]. Administration of SuperMApo has been shown to promote efferocytosis and inflammation resolution in acute and chronic inflammatory diseases [136, 137]. Therefore, SuperMApo represents a new approach to resolve inflammation.

Author contributions

Y.M. drafted the manuscript and prepared the figures. Y.M., S.S.K., X. Y., M.H.W., and S.Y.Y. edited the manuscript. S.Y.Y. directed and supported the work through all levels of development. All the authors

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Declarations of Competing Interest

None.

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